Creating genetic reports that are understood by non-specialists: a case study

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Abstract

Purpose—Guidelines recommend that genetic reports should be clear to non-specialists, including patients. We investigated the feasibility of creating reports for cystic fibrosis carrier testing through a rapid user-centered design process that built on a previously developed generic template. We evaluated the new reports' communication efficacy and effects on comprehension against comparable reports used in current clinical practice.

Methods—30 participants participated in 3 rounds of interviews. Usability problems were identified and rectified in each round. 193 participants participated in an evaluation of the resulting reports measuring subjective comprehension, risk probability comprehension, perceived communication efficacy, and other factors, as compared with standard reports.

Results—Participants viewing the user-centered reports rated them as clearer, easier to understand, and more effective at communicating key information than standard reports. Both groups ended up with equivalent knowledge of risk probabilities, although we observed differences in how those probabilities were perceived.

Conclusions—Our findings demonstrate that by starting with a patient-friendly generic report template and modifying it for specific scenarios with a rapid user-centered design process, reports can be produced that are more effective at communicating key information. The resulting reports are now being implemented into clinical care.

Keywords

genetic test reports; comprehension; user-centered design; risk communication; personalized medicine

Introduction

Genetic and genomic testing is becoming increasingly widely available due to falling costs of testing, new referral pathways, increased integration of such testing into mainstream clinical practice, and other initiatives such as the National Health Service (NHS) Long Term Plan and the "Improving Outcomes through Personalised Medicine" effort in the United Kingdom[1]. As access to such services expands, non-specialist clinicians are increasingly tasked with explaining the results of these tests to patients. In some cases, patients may be faced with the prospect of interpreting reports themselves without guidance. For example, patients in some countries can obtain copies of their test results directly from testing laboratories[2].

Research suggests that even clinicians have difficulties understanding genetic reports[3,4], and many researchers have recognized the need for clearer reports in light of variability among individuals in numeracy, health literacy, and genetic literacy[2,5,6]. Guidelines state that reports should be clear and comprehensible to non-specialists, and provide some guidance on how to achieve this[2,7–14]. Despite widespread adoption of some guidelines, such as those of the American College of Medical Genetics and Genomics (ACMG)[7], studies investigating patients' and non-specialists' satisfaction and perceptions find that existing reports leave substantial room for improvement[4,15–17]. Genomic reports are especially challenging due to lack of standardization[18,19] and the complexity and uncertainty of the information involved[20].

There have been attempts to make the interpretation of laboratory reports clearer to non-specialist clinicians[16,21–25], but far fewer to make them clearer to patients. In 2014, Haga et al.[2] noted that "only one study has described efforts to develop a patient-friendly pathology report" (p. 4). There have since been some efforts to make genetic or genomic test reports more patient-

friendly[2,14,26–30], including in the direct-to-consumer (DTC) industry[5,30]. However, work of this kind still appears rarely outside the DTC space, and there has been little published (or made publicly available) about the development of DTC reports. There are therefore few examples to guide the design and evaluation of a patient-friendly genetic report.

In industry, it is common for new products to be developed via a user-centered design[31,32] approach whereby changes are made in an iterative process, taking into account the context in which the product will be used, key requirements, and feedback from users. Typically, multiple rounds of evaluation are conducted, monitoring metric(s) of interest (e.g. number and severity of usability issues, time required for users to accomplish a task, etc.) to assess what changes are needed. The iterative process continues until some stopping criterion is reached.

With rare exceptions[25,28], user-centered design is not generally used as a guiding framework in the context of non-commercial genetic report development. Our aim was to determine whether such a process could be used to efficiently produce genetic report templates suitable for implementation. If such reports could be shown to communicate more effectively to laypersons, this would suggest a reasonable, cost-efficient approach that could be emulated by others.

Our approach was to split the design phase into two. In a first stage patients, non-specialist clinicians and genetic testing experts participated in the development of a report template for a fictional genetic condition. This work (submitted for publication) resulted in a generic template that could be adapted to specific use cases. We chose cystic fibrosis (CF) carrier testing as our specific use case as primary care physicians were being directed to order CF tests (and hence receive and communicate results) in our local healthcare region. There was therefore a need to ensure that reports from such testing were clear to non-specialist readers. Our study provides

preliminary findings regarding benefits and limits of what can be expected from a design process of this kind.

Materials and Methods

One design feature of the generic template was to accommodate the needs of both genetic specialists and non-specialists (including patients) by separating sections containing technical information from those in "plain English". Therefore, our reports had both a "patient-centered" page and a "clinician-centered" page, with the second page intended for health professionals.

Five two-page draft reports were developed representing common scenarios for CF carrier testing, where the reasons for referral were: partner heterozygous for p.Phe508del (positive and negative), familial p.Phe508del (positive and negative), and family history (unknown variant), negative report only. Reasons for referral were stated in simpler language on the patient-centered page of each report. Our initial reports were developed on the basis of our previously designed generic report template, with input from members of a working group who produced recommendations based on a revision of the ACGS general reporting guidelines. This group included members of the Regional NHS Clinical Genetics Laboratory in Cambridge, clinical geneticists, genetic counsellors, National External Quality Assessment Service members and other experts in the reporting of genetic test results.

User-centered testing can take a *formative* or *summative* approach. Formative testing is conducted iteratively while a product is still in development, whereas summative testing is done once the stopping criterion has been met and the design finalized. Their goals differ accordingly: whereas "formative testing focuses on identifying ways of making improvements, summative testing focuses on evaluating against a set of criteria"[33]. All five reports were subject to *formative*

testing, and two were selected for *summative testing*, namely those having "partner heterozygous for p.Phe508del" as the reason for referral (Figures S1-S2; sample patient-centered page in Figure 1). Corresponding anonymized "standard" report templates currently in use were obtained from Yorkshire and North East Genomic Laboratory Hub Central Laboratory to act as a control comparison (Figures S3-S4), with permission. Information that could have been used to identify the laboratory the templates came from was fictionalized. Informed consent was obtained from all participants. This study received ethical approval from the Cambridge Psychology Research Ethics Committee (PRE.2018.077).

User-centered design process

Interviews. Three rounds of semi-structured interviews were conducted over Skype with a convenience sample of 30 volunteers recruited from the Cambridge Rare Disease Network, individuals who had participated in previous studies, and researcher contacts. 12, 8, and 10 volunteers participated in each round, respectively. Volunteers were compensated with Amazon vouchers for £10. Interviews included questions pertaining to communication efficacy and subjective comprehension (e.g., questions about reports' appearance, structure, confusing language, etc.), objective comprehension, and actionability. Demographic information for participants in each round is summarized in Table S1.

Formative evaluation. The primary goal of the formative evaluation was to identify and address the most serious *usability problems* with the reports, borrowing the definition of Lavery et al.[34]: "an aspect of the system and/or a demand on the user which makes it unpleasant, inefficient, onerous or impossible for the user to achieve their goals in typical usage situations." Given that typical goals when receiving a genetic report are to (1) understand the contents and (2) to take

appropriate next steps if necessary (or to advise the patient of appropriate next steps), we treated as usability problems issues that caused confusion, left participants with incorrect impressions, generated unnecessary anxiety, or decreased the odds that a participant would be able to get the assistance they needed to take appropriate next steps. After rounds 2-3, interviewer notes and partial transcriptions of participants' answers to interview questions were reviewed and coded in MaxQDA to identify and evaluate the most significant problems, highlight cases of poor comprehension, and assess the degree to which the reports met participants' information needs. Full coding and partial transcription from interview recordings were completed post-hoc for Round 1, but interviewer notes were reviewed and usability problems were enumerated and corrected prior to round 2 nevertheless. Our stop criterion for how many rounds of interviewing to conduct was that by the final round, no major usability problems should remain. Major usability problems are those for which "the user will probably use or attempt to use the product, but will be severely limited in his or her ability to do so"[35]; we considered these to include issues that could leave recipients with a serious misconception.

Because we ultimately wished to run a summative evaluation focusing on *subjective comprehension, risk probability comprehension,* and *communication efficacy,* we categorized participant answers to questions intended to highlight usability issues that might affect these constructs in particular, as well as more exploratory constructs of interest (e.g., *actionability,* the degree to which "consumers of diverse backgrounds and varying levels of health literacy can identify what they can do based on the information presented"[36]). These questions were asked to help determine whether there were problems in any of these domains so severe as to constitute a major usability problem.

Summative evaluation. Interviews were followed by an experiment in which participants were given either the new (2-page) user-centered report or a standard (1 page) report currently in clinical use (and representative of standard practice). Our approach was to provide participants with the entire user-centered report, but to ask questions specific to the first page of the report to ensure that the patient-facing page was the one being evaluated. After receiving the participant information sheet, a consent form, and background information about cystic fibrosis, study participants were presented with a clinical scenario in which a hypothetical John and Jane Doe are thinking about starting a family. Neither has cystic fibrosis, but CF runs in Jane's family and she is known to be a carrier, so John's GP has advised him to have a carrier test to inform the couple's family planning decisions. Participants were then shown a copy of "John's report", a report filled in with fictional information about Mr. Doe, and asked to read it carefully. The report shown was either one of the standard reports described earlier, or one of the new user-centered reports. The evaluation therefore had a 2x2 factorial between-participants design with two levels of *design* (*standard* and *user-centered*) and two levels of *test result* (*positive* and *negative*). Afterwards, participants completed a questionnaire collecting outcome measures. On every questionnaire page, text stated: "Please answer the following based on what you have learned from the first page of the report. To take another look at it, you may click here"; clicking brought up the first page of the report. Note that basic background information about cystic fibrosis was provided to bring the experimental scenario closer to a typical real-world scenario. This was not done within the reports themselves, as in the real world a couple with CF in one partner's family would typically be aware of what CF is, particularly after meeting with a GP and being referred for testing.

Key outcomes were *subjective comprehension*, *risk probability comprehension*, and *communication efficacy*. Subjective comprehension was assessed by asking "How well did you understand the information in the first page of the report?" and "How clear is the information on the first page of the report?" on a seven-point scale ranging from 1 ("not at all") to 7 ("completely"). Risk probability comprehension was assessed by tallying the number of risk probability comprehension questions answered correctly out of seven presented, counting responses within ±1% of the correct answer as "correct." An investigator blinded to condition converted free-text responses to numbers. Communication efficacy was assessed using a version of the 18-item questionnaire developed by Scheuner et al.[16], modified so as to be appropriate for laypersons rather than clinicians (Table 1). A power analysis suggested 192 participants were required to achieve 80% power to detect an effect size *f* of .25 with intent to test main effects and two-way interactions via ANOVA. Alpha was adjusted to .01, two-tailed, permitting us to look for differences in the three key outcomes described earlier at an alpha of .05 with adjustment for multiple hypothesis testing. Normality of residuals was assessed using the Shapiro-Wilk test (α = .05).

ANOVA is fairly robust to violations of normality, but for severe violations nonparametric alternatives are sometimes applied. For example, the Mann-Whitney test compares the mean ranks of two samples, where the rank of a value is determined by ranking all values from low to high regardless of sample. Power analysis indicated that if this were used to compare the user-centered and standard reports on any of our key dependent variables, 192 participants would yield 78% power to detect a medium-sized effect (d = .5, α = .01). The Scheirer-Ray-Hare extension of the Kruskal Wallis test[37] is a nonparametric ANOVA alternative based on ranks

rather than means; 192 participants would provide 78% power to detect medium-sized main effects ($f = .25$, $\alpha = .01$).

48 participants were randomized by the Qualtrics survey distribution software to each combination of design (*standard* and *user-centered*) and *test result* (*positive* and *negative*), excepting *positive user-centered*, which had 49 due to a glitch with Prolific. "Difficult" risk probability comprehension questions always followed "easy" questions, but the order in which questions were presented was otherwise counterbalanced by question type (Table 2). Our minimum acceptable goal for the evaluation was to outperform the standard template on at least one key outcome without being inferior on the other two, although we hoped to outperform it significantly on all measures. Tests were two-sided with Bonferroni correction for multiple hypothesis testing. Measures of central tendency reported in the Results are means, unless otherwise stated.

A secondary goal was to achieve superiority on at least one measure (without being inferior on any measure), out of *all* measures recorded. This included not only key outcomes, but also five exploratory measures: *trust, actionability, risk probability interpretation, visibility of result summary,* and *ease of understanding the result summary*. *Trust* was assessed by asking "How much do you trust the information in the first page of the report?" on a 7-point scale from 1 ("not at all") to 7 ("completely"), and five questions related to *actionability* were included (Table 1). Two *risk probability interpretation* questions were included— "Is John a carrier of cystic fibrosis?" and "If John and Jane have a child, will the child have cystic fibrosis?"—with multiple-choice answers (*definitely not, unlikely, likely,* and *definitely*). This provides insight into how people understand the numbers, but we had no goal beyond ensuring that viewers of positive reports did not conclude that the couple would "definitely" or "definitely not" have a

child with CF, and that viewers of negative reports did not conclude that the couple would "likely" or "definitely" have a child with CF. This is because there is no right answer with respect to whether a 25% chance of having a child with cystic fibrosis feels "unlikely" or all too "likely." Participants were asked whether they had noticed the result summary (the "Your Result" box for the user-centered report, or the analogous "Summary" statement for the standard report) and how easy the result was to understand (from 1 "not at all easy" to 7 "very easy"). Finally, subjective numeracy[38] was collected, as well as demographic information.

Code availability

Code and data for primary analyses, as well as additional exploratory analyses not reported here, are available at https://github.com/WintonCentre/cf_reports (ver. 2019.07.22).

Results

Formative evaluation

Quantitative summaries of participant responses to questions relating to subjective comprehension, risk probability comprehension, communication efficacy, and actionability are provided in Figures S5-S9 and Table S3. Answers to these questions suggested adequate comprehension of the version 3 reports, at least in our small sample of ten participants (Table S3). A summary of changes made after each round of testing is available in Tables S4-S5, and qualitative description of usability problems in each round and severity classifications are given in Table S6, with nothing rising to the level of a major usability problem by the final round. Formative evaluation was therefore stopped at this point and a summative evaluation was conducted for the version 3 partner reports. A full analysis of all substantive participant

comments is beyond the scope of this paper, but a few examples of how specific usability issues led to specific changes are detailed in Table S7.

One issue noted during Round 3 was that multiple participants commented that they had not noticed the result summary box on their first read-through. This did not rise to the level of a usability problem as these participants all read and understood the description of the result in the "What This Result Means For You" section, but it was of sufficient concern that *visibility of result summary* was added to the summative evaluation as an exploratory measure.

Summative evaluation

193 participants were paid £1.96/person to complete the study via Prolific Academic; demographic characteristics appear in Table S2. Due to violations of normality, Mann-Whitney U-tests were used rather than ANOVAs, comparing mean ranks between the two conditions.

Subjective comprehension was higher for the user-centered (UC) reports, whether participants were asked about *understanding* (M_{UC} = 5.74, SD_{UC} = 1.18, $M_{standard}$ = 4.94, $SD_{standard}$ = 1.23, U = 2896, p < .001, d = .7) or *clarity* (M_{UC} = 5.78, SD_{UC} = 1.20, $M_{standard}$ = 4.65, $SD_{standard}$ = 1.31, U = 2322, p < .001, d = .9). No differences were observed in *risk probability comprehension* (M_{UC} = 4.95, SD_{UC} = 2.30, $M_{standard}$ = 4.94, $SD_{standard}$ = 2.31, U = 4618, p = .9, d = 0.0), and item-wise chi-squared tests revealed that no questions in Table 2 were answered correctly more frequently in one condition than the other. Like Scheuner et al.[16], we compared the mean total scores on *communication efficacy*, finding higher scores for the user-centered reports (M_{UC} = 3.11, SD_{UC} = 0.56, $M_{standard}$ = 2.41, $SD_{standard}$ = 0.7, U = 2045, p < .001, d = 1.1). Item-wise analyses found significant differences for each item in favor of the user-centered reports, all p < .001 (Table 1). Analogous U-tests comparing *positive* vs *negative* reports were conducted, none of which found significant results.

User-centered reports trended slightly higher with respect to trust (M_{UC} = 6.23, SD_{UC} = .99, $M_{standard}$ = 5.92, $SD_{standard}$ = 1.12, U = 3874, p = .03, d = .3), non-significant after correction for multiple hypothesis testing. They were reliably higher on *actionability* (M_{UC} = 5.41, SD_{UC} = 1.20, $M_{standard}$ = 4.37, $SD_{standard}$ = 1.47, U = 2733, p < .001, d = 0.8), with item-wise analyses favoring the new reports on every question (Table 1). Surprisingly, 27% reported that they had not noticed the result summary in the user-centered reports versus 8% in the standard reports, X^2(1, N = 193) = 10.1, p = .001. However, estimates of John's probability of being a carrier (Table 2, Question 2) were no different, suggesting that this information was clear even to those who missed the summary (positive reports: median 100% both conditions, M_{UC} = .86, SD_{UC} = .29, $M_{standard}$ = .80, $SD_{standard}$ = .32, U = 1170, p > .9, d = .2; negative reports: median 1% both conditions, M_{UC} = .07, SD_{UC} = .16, $M_{standard}$ = .07, $SD_{standard}$ = .16, U = 1161, p > .9, d = 0.0). The user-centered reports' result summaries were also rated easier to understand, M_{UC} = 6.05, SD_{UC} = 1.33, $M_{standard}$ = 5.00, $SD_{standard}$ = 1.66, U = 2876, p < .001, d = .7.

When estimating the probability that the first child would have cystic fibrosis (Table 2, Question 4), there were no significant differences between levels of *design* for either positive reports (median 25% both conditions; M_{UC} = .31, SD_{UC} = .16, $M_{standard}$ = .33, $SD_{standard}$ = .19, U = 1328, p = .2, d = -.2) or negative reports (median 1% both conditions; M_{UC} = .10, SD_{UC} = .17, $M_{standard}$ = .06, $SD_{standard}$ = .11, U = 1100, p = .8, d = .3). Nevertheless, responses to the risk interpretation questions suggested possible differences in the *interpretation* of these numbers (Figure 2) for those who had been shown the positive reports, with those who saw the user-centered positive report more apt to say that a child of two carriers was "unlikely" to have cystic fibrosis than those who saw the standard positive report, X^2(1, N = 97) = 7.8, p = .005. Overall performance with respect to the goals of the evaluation is summarized in Table S8.

Despite the violations of normality, 2x2 ANOVAs crossing *design* with *test result* as well as the Scheirer-Ray-Hare extension of the Kruskal Wallis test were also run on our key dependent measures. In both cases the same main effects were found, with no significant interactions.

Discussion

Our findings suggest that by starting with a patient-friendly generic report template and modifying it for a specific genetic test with a rapid user-centered design process, reports can be made that laypersons find significantly clearer, easier to understand, and more effective at communicating key information, including what they should do next (actionability). The improvements in actionability are particularly encouraging, as several interview participants noted that it is especially important that patients feel they understand "next steps", and that they feel they have adequate information and support to make follow-up decisions. We also saw cautions from the risk comprehension literature[39] borne out in our qualitative results (Table 3). Although we found no differences in risk probability comprehension, performance was near ceiling, with a median of 6 out of 7 questions correct for both the user-centered and standard reports. Furthermore, combining user-centered testing with quantitative evaluation led us to insights that would have been difficult to achieve without both methods. For example, some individuals noted that although they understood their results from reading the text of the report, they had missed the summary box titled "Your Result". Therefore, we added a question investigating this to our quantitative evaluation, which confirmed that 27% of participants did not remember seeing this box. Thus, even anecdotal evidence from small qualitative studies can generate important hypotheses that can then be tested more rigorously.

One limitation of our formative evaluation was that participants were overwhelmingly female (80%) and highly educated (Table S1). Our summative evaluation sample had similar biases

(~69% female, ~56% university-educated), among other differences from the UK population (Table S2). Although subgroup analysis demonstrated that the benefits of our novel templates were thankfully not restricted to women, nor to the highly educated or highly numerate (Table S9), our development process could have identified important issues more quickly if we had solicited input from a more diverse group of participants from the outset. Given this non-representative sample and the fact that it was more difficult to see the result summary in our report than in the standard report, we have made one additional change to address this, and are planning a replication of our summative evaluation with this new report using census-matched cross-stratified quota sampling.

Another drawback is that the use of a hypothetical scenario with our testing group means that our results are less likely to generalize than if they had been conducted as part of a clinical study. (See Stuckey et al. 2015[26], Williams et al. 2018[28] for examples of patient-facing work that does not suffer from this limitation.) Furthermore, this study was limited to a single autosomal recessive condition. We have planned future research on reports for *BRCA1/BRCA2* testing, which will investigate whether the benefits of this approach generalize to material that is more challenging to communicate.

Overall, our experience demonstrated that a user-centered approach can be extremely helpful in discovering and rectifying usability problems with genetic reports. We hope that this research illustrates how rapid user-centered design can be used to develop more comprehensible and actionable reports, and that building on templates developed via user-centered design may be useful in developing patient-facing materials more generally.

Acknowledgements

This work was supported by the David & Claudia Harding Foundation via the Winton Centre for Risk and Evidence Communication, sponsored by the University of Cambridge. The second author is funded by Health Education England. The authors would also like to thank George Farmer, Harry Gray, Yorkshire and North East Genomic Laboratory Hub Central Laboratory, Beverley Speight (Principal Genetic Counsellor, Cambridge University Hospitals NHS Foundation Trust), Ed Thompson, Steve Abbs, and Leila Finikarides.

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Figure Legends

Figure 1. Patient-friendly page of user-centered “Positive / Partner p.Phe508del” report.

Figure 2. Responses given by participants who viewed reports with positive test results to the question “If John and Jane have a child, will the child have cystic fibrosis?” When asked to produce the numeric probability that the first child would have cystic fibrosis (Table 2, Section 4), participants who felt it was “likely” that the first child would have cystic fibrosis had mean estimates of 34% (SD = 21%) if they had seen the standard report, compared to 31% (SD = 12%) if they had seen the user-centered report (no significant difference, U = 473, p = .7). Participants who felt it was “unlikely” that the first child would have cystic fibrosis had mean estimates of 25% (SD = .4%) if they had seen the standard report, compared to 27% (SD = 14%) if they had seen the user-centered report (no significant difference, U = 100, p = .4).

Conflict of interest notification page

None of the authors have conflicts of interest to report. Dr Gemma Chandratillake owns shares in companies related to genetics (Personalis, Petagene), as does her husband (Sophia Genetics); none of these companies are involved in CF reporting. This research was funded by the David & Claudia Harding Foundation via the Winton Centre for Risk and Evidence Communication at the University of Cambridge. The second author is funded by Health Education England (Genomics Education Programme).

Figure 1

GENETIC TEST REPORT

NHS

Patient Details:

Name:	John Doe
Date of birth:	18 March 1995
Sex:	Male
NHS number:	NH00198
Sample type:	Blood

Test ordered by:

Name:	Dr Requesta
Organisation:	Alesford Hospital
Telephone:	01238 555555
Copies to:	Dr A. Nother Dr X. Tra

Test carried out by:

Laboratory:	Acurogen UK
Telephone:	01238 666555
Date received:	26 February 2018
Date reported:	12 March 2018
Authorised by:	A Tester

Reason for test: CF carrier status testing requested. Partner is a carrier of CF.

Your Result	Carrier of cystic fibrosis

ABOUT THE TEST

This test looked at a gene called CFTR. Everyone has two copies of this gene (one from their mother and one from their father). Alterations to this gene can cause the condition cystic fibrosis (CF).

If you have an alteration in **both** copies of your CFTR genes you will have CF.
If you have an alteration in **only one** copy of CFTR you will not have CF but will be a '**carrier**'.
Carriers are healthy but may pass on their altered gene to any children.

WHAT THIS RESULT MEANS FOR YOU

The test found that you have an alteration in one copy of your CFTR genes, making you a carrier of CF.

If you have children with someone who is also a carrier of CF, there is a 1 in 4 (25%) chance in **each pregnancy** that the child will have CF.

If you have children with someone who has not been tested for CF, there is less than 1 in 100 (less than 1%) chance that those children will have CF (some risk remains as your partner may be a carrier but not know).

In the UK population, around 1 in 25 (4%) people are carriers of CF. Because you are a carrier of CF, your close relatives have an increased chance of also being CF carriers, so carrier testing can now be offered to your adult relatives.

NEXT STEPS

- **You can be referred to the Clinical Genetics Service to discuss your options when planning a family. Please ask your doctor for this referral if it has not been made. Take this report with you to any appointments.**
- **If your relatives would like to be tested, they should ask their GP about CF carrier testing.**

MORE INFORMATION AND SUPPORT

The results of a genetic test can be upsetting and difficult to take in.

If you have questions about your test result, talk to the doctor who ordered your test or phone the East Anglian Clinical Genetics Service on 01238 216446 . Your doctor can also phone this number for advice and to help answer your queries.

To understand more about genetic testing, visit: www.nhs.uk/conditions/genetics/services/

To understand more about cystic fibrosis, visit: www.cysticfibrosis.org.uk/ or phone 01238 373 100

Figure 2

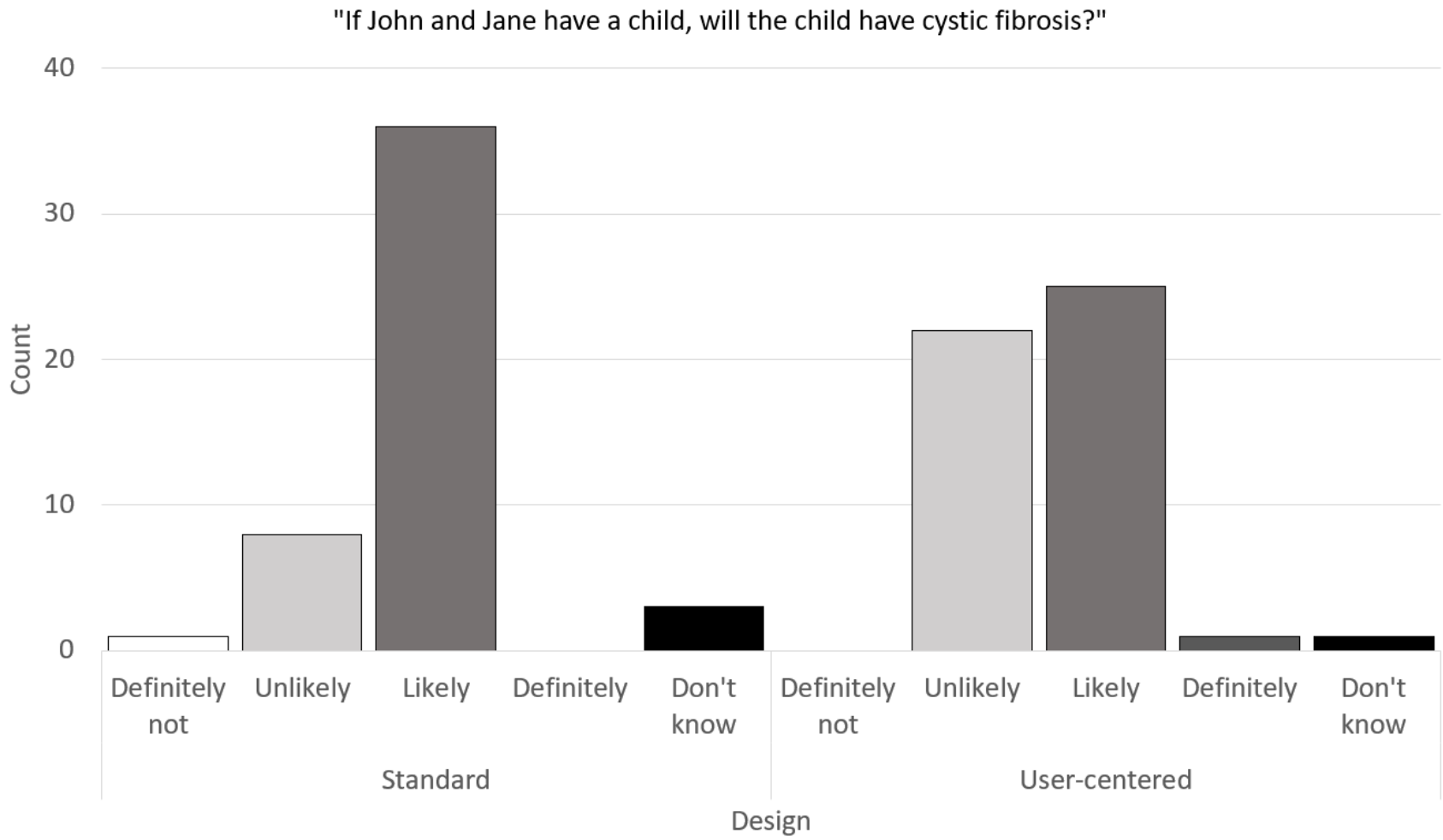
"If John and Jane have a child, will the child have cystic fibrosis?"
40
30
20
10
0
Count
Definitely not
Unlikely
Likely
Definitely
Don't know
Definitely not
Unlikely
Likely
Definitely
Don't know
Standard
User-centered
Design

Table 1

Table 1. Scores for the standard and user-centered reports.[a]

	Standard report		User-centered report		
	Mean	SD	Mean	SD	p-value
Subjective comprehension, clarity, trust (7-point scale)					
How well did you understand the information…	4.94	1.23	5.74	1.18	<.001
How clear is the information…	4.65	1.31	5.78	1.20	<.001
How much do you trust the information…	5.92	1.12	6.23	0.99	.03
Communication efficacy (4-point scale modified from Scheuner et al, 2013)					
How satisfied are you with…					
The general format (look and feel) …	2.62	0.90	3.31	0.71	<.001
The amount of information…	2.83	0.83	3.38	0.73	<.001
The organization of the information…	2.68	0.88	3.29	0.71	<.001
How easy is it to…					
Find the test result…	2.67	0.95	3.35	0.78	<.001
Find information… to help with decision making?	2.42	0.90	3.10	0.78	<.001
Understand the language used…	2.35	0.88	3.25	0.78	<.001
Understand the test result presented…	2.53	0.89	3.34	0.76	<.001
Understand the interpretation of the test result…	2.56	0.90	3.13	0.80	<.001
How effectively does the first page of the report…					
Communicate the test result?	2.67	0.88	3.38	0.73	<.001
Communicate what this test result means?	2.47	0.98	3.23	0.67	<.001
Communicate the patient's options (i.e., John's options) having received this test result?	2.16	1.00	2.94	0.79	<.001
Communicate the availability of information resources for the patient (i.e., John)?	1.98	0.96	2.95	0.86	<.001
Communicate the availability of information resources for health professionals (i.e., John's GP)?	2.10	0.92	2.87	0.82	<.001
Inform medical decisions the patient (i.e., John) might have to make as a result of this test?	2.46	0.99	3.01	0.74	<.001
Help you explain what the test result means to other people?	2.42	0.93	3.00	0.88	<.001
Help you understand the medical issues relating to the result?	2.27	0.90	2.81	0.89	<.001
Help you understand the genetic aspects of the result?	2.40	0.93	2.97	0.85	<.001
Communicate any limitations of the test result?	1.83	0.83	2.69	0.96	<.001
Actionability (7-point scale)					
How clear are you about the next steps that you could take…	4.40	1.60	5.53	1.35	<.001
Do you feel you would have the necessary information to decide what to do next…	4.26	1.71	5.21	1.52	<.001
How certain are you about what you would do next…	4.49	1.75	5.62	1.32	<.001
Do you feel you would have the necessary professional support to decide what to do next…	4.45	1.53	5.47	1.30	<.001
How ready would you feel to take any next steps…	4.27	1.72	5.21	1.38	<.001

[a]To make the table more compact, ellipses ("…") appearing in communication efficacy questions and subjective understanding/clarity/trust questions stand in for the phrase "in the first page of the report" ("of the first page of the report," communication efficacy question 1). Ellipses appearing in actionability questions stand in for the phrase "if you had received this report in real life."

Table 2

Table 2. Measures of participant comprehension of risk probabilities.

Question ID/type and difficulty	Question	Answer format
Q1/Carrier risk (easy)	What do you think the probability is that John is a carrier of cystic fibrosis? You can indicate this probability as a percentage, or in another way if you prefer.	Free text
Q2/Carrier risk (easy)	Please indicate the probability that John is a carrier of cystic fibrosis by dragging the slider below. [a]	Probability slider from "0% chance" to "100% chance"
Q3/Risk to child (easy)	If John and Jane have a child, what do you think the probability is that the child will have cystic fibrosis? You can indicate this probability as a percentage, or in another way if you prefer.	Free text
Q4/Risk to child (easy)	Please indicate the probability that the child will have cystic fibrosis by dragging the slider below. [a]	Probability slider from "0% chance" to "100% chance"
Q5/Risk to child (hard)	Imagine that there are 1000 couples in exactly the same situation as John and Jane: that is to say, o one partner is a carrier (like Jane is), and o the other partner has had the same test that John has had, and received the same result as John did. If each of these 1000 couples have one child, about how many of these 1000 children would have cystic fibrosis? If you aren't sure, or if you think there are many possibilities, please make your **best guess** as to the **most likely** number of children to have cystic fibrosis, from 0 to 1000.	Free text; single number expected
Q6/Risk to child (hard)	[As above with "800" in place of "1000"]	Free text; single number expected
Q7/Both risks	Which of the following possibilities is more likely? o John Doe is a carrier of cystic fibrosis o The first child of John and Jane Doe will have cystic fibrosis	Multiple choice: • It's more likely that John Doe is a carrier of cystic fibrosis • It's more likely that the first child of John and Jane Doe will have cystic fibrosis • Both possibilities are equally likely • Don't know

[a]The following text followed in both cases: "If you aren't sure, please make your best guess. If you can't mark exactly the probability you want using the slider, please put it as close to that probability as you can."

Table 3. Recommendations and lessons learned.

Topic	Recommendation
Design	Splitting the design process into two phases—one to develop a generic template with key sections and information that patients want from the results, and one to populate that template with the specific numbers and information for each type of test—may provide an efficient way to produce large numbers of report templates for medical test results. Test with users: recommendations from the literature should not be applied blindly. For example, although there are good reasons to present risk figures in multiple formats as a general rule, in our case including "1 in 25 (4%)" and "1 in 4 (25%)" in close proximity caused confusion. User testing permitted us to address the issue in a way that allowed us to continue following the recommendation but also eliminated the confusion. Focus on recruitment of diverse representative end users throughout the process. We benefited from multiple perspectives of different user groups (healthcare providers, patients, and members of the public with varying levels of experience of genetic testing), and would have benefited from a more concerted effort to recruit participants who were more diverse in other ways (e.g. education).
Evaluation	Following up on comments from interviews with a larger sample size can be a useful way to determine whether an offhand comment ("I don't know how I missed that!") is indicative of a larger issue (27% of participants indicating that they did not see the result summary box). Formative and summative evaluation both ought to be applied to important patient-facing materials whenever possible.
Vocabulary and Wording	When using vocabulary that implies a change in risk (e.g. reduce/increase), the risks being compared must be clearly described. For patient-facing materials, "gene changes" is a poor plain-English alternative to "variant," as it sometimes led to misinterpretations (e.g., "What does it mean by no cystic fibrosis gene changes detected? Can genes change throughout the life course or something? I thought you're kind of born with it or you're not.") In our study, "alterations" seemed to be reasonably well received and interpreted. Prior literature[39] has found that a quarter of people incorrectly answer the question "Which of the following numbers represents the biggest risk of getting a disease? 1 in 100, 1 in 1000, or 1 in 10?", not realizing that a larger number in the denominator corresponds to a smaller probability. A quote from one of our participants suggested she had a similar misapprehension ("*less* than 1 in 500 sounds less scary, because then you can think, oh, it could be 400 or 200"). When presenting probabilities that are intended to be compared with each other, keep denominators constant to decrease the chances of misinterpretation, i.e., compare *1 in 1000* to *6 in 1000* rather than comparing *1 in 1000* to *1 in 167*.

Figure S1

User-centered “Positive / Partner p.Phe508del” report.

GENETIC TEST REPORT

NHS

Patient Details:

Name:	John Doe
Date of birth:	18 March 1995
Sex:	Male
NHS number:	NH00198
Sample type:	Blood

Test ordered by:

Name:	Dr Requesta
Organisation:	Alesford Hospital
Telephone:	01238 555555
Copies to:	Dr A. Nother Dr X. Tra

Test carried out by:

Laboratory:	Acurogen UK
Telephone:	01238 666555
Date received:	26 February 2018
Date reported:	12 March 2018
Authorised by:	A Tester

Reason for test: CF carrier status testing requested. Partner is a carrier of CF.

Your Result — **Carrier of cystic fibrosis**

ABOUT THE TEST

This test looked at a gene called CFTR. Everyone has two copies of this gene (one from their mother and one from their father). Alterations to this gene can cause the condition cystic fibrosis (CF).

If you have an alteration in **both** copies of your CFTR genes you will have CF.
If you have an alteration in **only one** copy of CFTR you will not have CF but will be a '**carrier**'.
Carriers are healthy but may pass on their altered gene to any children.

WHAT THIS RESULT MEANS FOR YOU

The test found that you have an alteration in one copy of your CFTR genes, making you a carrier of CF.

If you have children with someone who is also a carrier of CF, there is a 1 in 4 (25%) chance in **each pregnancy** that the child will have CF.

If you have children with someone who has not been tested for CF, there is less than 1 in 100 (less than 1%) chance that those children will have CF (some risk remains as your partner may be a carrier but not know).

In the UK population, around 1 in 25 (4%) people are carriers of CF. Because you are a carrier of CF, your close relatives have an increased chance of also being CF carriers, so carrier testing can now be offered to your adult relatives.

NEXT STEPS

- **You can be referred to the Clinical Genetics Service to discuss your options when planning a family. Please ask your doctor for this referral if it has not been made. Take this report with you to any appointments.**
- **If your relatives would like to be tested, they should ask their GP about CF carrier testing.**

MORE INFORMATION AND SUPPORT

The results of a genetic test can be upsetting and difficult to take in.

If you have questions about your test result, talk to the doctor who ordered your test or phone the East Anglian Clinical Genetics Service on 01238 216446 . Your doctor can also phone this number for advice and to help answer your queries.

To understand more about genetic testing, visit: www.nhs.uk/conditions/genetics/services/

To understand more about cystic fibrosis, visit: www.cysticfibrosis.org.uk/ or phone 01238 373 100

GENETIC TEST REPORT

NHS

Technical Information

Patient Details:

Name:	John Doe
Date of birth:	18 March 1995
Sex:	Male
NHS number:	NH00198
Sample type:	Blood

Sample collected: 10 March 2018
Sample received: 12 March 2018

For Your Records — **The information on this page is for health professionals. It is not essential that patients read this section.**

Gene	Zygosity	Inheritance	HGVS Description	Location	Classification
CFTR	Heterozygous	Autosomal recessive	NM_000492.3: c.1521_1523delCTT p.(Phe508del) GRCh37(hg19)	Chr7: g.117199646_117199648del	Pathogenic

Full Interpretation

John Doe's Partner, Jane (d.o.b. 28/09/2004) is a carrier of cystic fibrosis (CF) and is heterozygous for the common c.1521_1523delCTT p.(Phe508del) cystic fibrosis gene (CFTR) variant (information received with referral).

John Doe is heterozygous for the c.1521_1523delCTT p.(Phe508del) CFTR gene variant and is therefore a carrier of CF.

The risk of John Doe and Jane having a child with CF is 1 in 4 (25%) for each pregnancy. Prenatal diagnostic testing can be offered to this couple via referral to Clinical Genetics.

Carrier testing for the c.1521_1523delCTT p.(Phe508del) CFTR gene variant may be offered to John Doe's close relatives. For CF cascade testing in the East Anglian region, GPs can send a blood sample direct to the Regional Genetics Laboratory (www.cuh.nhs.uk/clinical-genetics). Relatives of the patient who live outside of East Anglia should ask their GP how testing is carried out locally.

Test Methodology

CF-EU2v1 Elucigene Assay (http://www.elucigene.com/product/cfeu2v1/) includes 50 of the most frequently observed European CF pathogenic variants - see our website (http://cuh.org.uk/genetics-labs-cf) for variant details. Variant nomenclature is in accordance with the Human Genome Variation Society (HGVS) guidelines according to GenBank accession number NM_000492.3 (DNA) and NP_000483.3 (protein) where +1 is the A of the ATG translation initiation codon.

Risk of a false positive: 0.1%

Risk of a false negative: 0.1%

References:

World Health Organization (WHO), 2004. The molecular epidemiology of cystic fibrosis. Available: http://www.who.int/genomics/publications/reports/en/

McCormick et al. 2002 Eur J Hum Genet. 2002 Oct;10(10):583-90.

Figure S2

User-centered “Negative / Partner p.Phe508del” report.

GENETIC TEST REPORT

NHS

Patient Details:

Name: John Doe
Date of birth: 18 March 1995
Sex: Male
NHS number: NH00198
Sample type: Blood

Test ordered by:

Name: Dr Requesta
Organisation: Alesford Hospital
Telephone: 01238 555555
Copies to: Dr A. Nother
Dr X. Tra

Test carried out by:

Laboratory: Acurogen UK
Telephone: 01238 666555
Date received: 26 February 2018
Date reported: 12 March 2018
Authorised by: A Tester

Reason for test: CF carrier status testing requested. Partner is a carrier of CF.

Your Result — **No common cystic fibrosis gene alterations detected**

ABOUT THE TEST

This test looked at a gene called CFTR. Everyone has two copies of this gene (one from their mother and one from their father). Alterations to this gene can cause the condition cystic fibrosis (CF).

If you have an alteration in **both** copies of your CFTR genes you will have CF.
If you have an alteration in **only one** copy of CFTR you will not have CF but will be a '**carrier**'.
Carriers are healthy but may pass on their altered gene to any children.

WHAT THIS RESULT MEANS FOR YOU

Your sample has been tested for the common alterations to the CTFR gene that cause CF. No alterations were detected, so you are not a carrier of any of the alterations we tested for.

There are many alterations to the CFTR gene that are known to cause CF but some are very rare. This test looks for almost all of the alterations seen in the UK population.

The fact that the test did not detect any alterations means the chance that you carry a CFTR gene alteration is around 6 in 1000 (0.6%): there is still a very small possibility that you have one of the rare alterations. However, this is highly unlikely if there is no-one in your family who has CF.

If you have children with someone who is a carrier of CF, there is a less than 2 in 1000 (0.16%) chance in **each pregnancy** that the child will have CF.

NEXT STEPS

- **You do not need to do anything as a result of this test, but if you have questions about it, talk to your doctor.**

MORE INFORMATION AND SUPPORT

The results of a genetic test can be upsetting and difficult to take in.

If you have questions about your test result, talk to the doctor who ordered your test or phone the East Anglian Clinical Genetics Service on 01238 216446. Your doctor can also phone this number for advice and to help answer your queries.

To understand more about genetic testing, visit: www.nhs.uk/conditions/genetics/services/

To understand more about cystic fibrosis, visit: www.cysticfibrosis.org.uk/ or phone 01238 373 100

GENETIC TEST REPORT

NHS

Technical Information

Patient Details:

Name: John Doe
Date of birth: 18 March 1995
Sex: Male
NHS number: NH00198
Sample type: Blood

Sample collected: 10 March 2018
Sample received: 12 March 2018

For Your Records — **The information on this page is for health professionals. It is not essential that patients read this section.**

Gene	Zygosity	Inheritance	HGVS Description	Location	Classification
CFTR	No variant	Not applicable	NM_000492.3: c.1521_1523delCTT p.(Phe508del) GRCh37(hg19)	Not applicable	Not applicable

Full Interpretation

John Doe's Partner, Jane (d.o.b. 28/09/2004) is a carrier of cystic fibrosis (CF) and is heterozygous for the common c.1521_1523delCTT p.(Phe508del) cystic fibrosis gene (CFTR) variant (information received with referral).

DNA from John Doe has been tested for the common c.1521_1523delCTT p.(Phe508del) CFTR gene variant as well as other CFTR variants (see below) which together account for approximately 85% of UK CFTR gene variants (WHO, 2004). No CFTR gene variants were detected by our test.

This reduces John Doe's CF carrier risk to 1 in 161 (0.6%).

Test Methodology

CF-EU2v1 Elucigene Assay (http://www.elucigene.com/product/cfeu2v1/) includes 50 of the most frequently observed European CF pathogenic variants - see our website (http://cuh.org.uk/genetics-labs-cf) for variant details. Variant nomenclature is in accordance with the Human Genome Variation Society (HGVS) guidelines according to GenBank accession number NM_000492.3 (DNA) and NP_000483.3 (protein) where +1 is the A of the ATG translation initiation codon.

Risk of a false positive: 0.1%

Risk of a false negative: 0.1%

References:

World Health Organization (WHO), 2004. The molecular epidemiology of cystic fibrosis. Available: http://www.who.int/genomics/publications/reports/en/

McCormick et al. 2002 Eur J Hum Genet. 2002 Oct;10(10):583-90.

Figure S3

Standard “Positive / Partner p.Phe508del” report.

Acurogen Genetics Laboratory

101 Long Street, Alesford, Devon, AS1 1AB, UK

Website: www.acurogen.co.uk
Email: info@acurogen.co.uk

Clinical Service Lead:
Dr H Ead PhD FRCPath

Tel: 01238 555666
Fax: 01238 666555

Report of Molecular Genetic Analysis for Cystic Fibrosis

Patient name:	DOE John	Referred by:	Dr Requesta
		Unit:	
DOB:	18 Mar 1995	Date requested:	26 Feb 2018
Sex:	Male		
NHS No.:	NH00198	Acurogen Pedigree:	
Unit no.:	Not provided	Acurogen Lab no:	
Sample type:	Blood		
Test reason:	Partner is a CF carrier (information provided with referral; no further information available). This patient is assumed to be at ~1 in 25 prior risk of being a CF carrier (population carrier risk). The prior risk to any future child of this patient and their partner of being affected with CF is ~1 in 100. Carrier test.		

Results and Interpretation:

Test	Result	Lab Ref
CF-EU2v1	**c.1521_1523del heterozygote**	ACU55-5555

CF-EU2v1 analysis indicates that this patient is heterozygous for the pathogenic CFTR mutation c.1521_1523del p.(Phe508del). The remaining CFTR mutations tested for by the CF-EU2v1 kit are absent. This patient is therefore a CF carrier. The risk to any future child of this patient and their partner of being affected with CF is increased to 1 in 4. Assuming that this patient's partner has an identified CFTR mutation, prenatal CF testing is available if appropriate. We strongly recommend that this patient and their partner are referred to their local Clinical Genetics department.

This result also has important implications for relatives of this patient, and testing is available if appropriate. We recommend that these individuals are referred to their local Clinical Genetics department.

Summary:

This patient is heterozygous for the pathogenic CFTR mutation c.1521_1523del, and is therefore a CF carrier. The risk to any future child of this patient and their partner of being affected with CF is increased to 1 in 4.

Reported: Dr A Filer — *Clinical Scientist*

Authorised: Dr A Tester — *Principal Clinical Scientist*

Date: 12 Mar 2018

All reports depend upon the diagnosis of affected individuals, identification of samples and biological relationships of the individuals being correct.

Notes: Germline mutations within the CFTR gene cause cystic fibrosis (CF) or a CFTR-related disorder (CFTR-RD), which have autosomal recessive inheritance. The CF-EU2v1 (Elucigene) kit uses fluorescent ARMS (Amplification Refractory Mutation System) allele-specific amplification technology to identify 50 CFTR point mutations, insertions, or deletions. Please see the laboratory website (http://www.acurogen.co.uk) for a list of these 50 mutations, including previous nomenclature. In the local Caucasian population these mutations account for approximately 88% of all CF alleles. CFTR mutations are named according to HGVS (www.hgvs.org) guidelines using the reference sequence NM_000492.3. Very rare variants within the CFTR gene may interfere with the CF-EU2v1 assay, causing false positive or false negative results.
Please see the laboratory website (http://www.acurogen.co.uk) for further information regarding CFTR analysis.

References:
Schwarz et al. Cystic fibrosis mutation analysis: Report from 22 UK regional genetics laboratories. Hum Mutat. 1995;6(4):326-33
McCormick et al. Demographics of the UK cystic fibrosis population: Implications for neonatal screening. Eur J Hum Genet. 2002 Oct;10(10):583-90

Figure S4
Standard “Negative / Partner p.Phe508del” report.

Acurogen Genetics Laboratory

101 Long Street, Alesford, Devon, AS1 1AB, UK

Website: www.acurogen.co.uk
Email: info@acurogen.co.uk

Clinical Service Lead:
Dr H Ead PhD FRCPath

Tel: 01238 555666
Fax: 01238 666555

Report of Molecular Genetic Analysis for Cystic Fibrosis

Patient name:	DOE John	Referred by:	Dr Requesta
		Unit:	
DOB:	18 Mar 1995	Date requested:	26 Feb 2018
Sex:	Male		
NHS No.:	NH00198	Acurogen Pedigree:	
Unit no.:	Not provided	Acurogen Lab no:	
Sample type:	Blood		

Test reason: Partner is a CF carrier (information provided with referral; no further information available). This patient is assumed to be at ~1 in 25 prior risk of being a CF carrier (population carrier risk). The prior risk to any future child of this patient and their partner of being affected with CF is ~1 in 100.
Carrier test.

Results and Interpretation:

Test	Result	Lab Ref
CF-EU2v1	**c.1521_1523del heterozygote**	ACU55-5555

Analysis indicates that the 50 CFTR mutations tested for by the CF-EU2v1 kit are absent in this patient. This result reduces this patient's CF carrier risk to ~1 in 200. The risk to the first child of this patient and their partner, Jane Doe, of being affected with CF is therefore reduced to ~1 in 800. Prenatal testing is not indicated.

Summary:

This patient's CF carrier risk is reduced to ~1 in 200. The risk to the first child of this couple of being affected with CF is reduced to ~1 in 800.

Reported: Dr A Filer — *Clinical Scientist*

Authorised: Dr A Tester — *Principal Clinical Scientist*

Date: 12 Mar 2018

All reports depend upon the diagnosis of affected individuals, identification of samples and biological relationships of the individuals being correct.

Notes: Germline mutations within the CFTR gene cause cystic fibrosis (CF) or a CFTR-related disorder (CFTR-RD), which have autosomal recessive inheritance. The CF-EU2v1 (Elucigene) kit uses fluorescent ARMS (Amplification Refractory Mutation System) allele-specific amplification technology to identify 50 CFTR point mutations, insertions, or deletions. Please see the laboratory website (http://www.acurogen.co.uk) for a list of these 50 mutations, including previous nomenclature. In the local Caucasian population these mutations account for approximately 88% of all CF alleles. CFTR mutations are named according to HGVS (www.hgvs.org) guidelines using the reference sequence NM_000492.3. Very rare variants within the CFTR gene may interfere with the CF-EU2v1 assay, causing false positive or false negative results.
Please see the laboratory website (http://www.acurogen.co.uk) for further information regarding CFTR analysis.

References:

Schwarz et al. Cystic fibrosis mutation analysis: Report from 22 UK regional genetics laboratories. Hum Mutat. 1995;6(4):326-33
McCormick et al. Demographics of the UK cystic fibrosis population: Implications for neonatal screening. Eur J Hum Genet. 2002 Oct;10(10):583-90

Figure S5

Participant answers to the question “Is the patient given enough guidance about the implications of the result and what actions they could now take?” were coded by 3 independent raters (Fleiss’ kappa 0.6) into the categories indicated in the legend. Visualisation on left panel includes all participants, while right panel excludes healthcare providers.

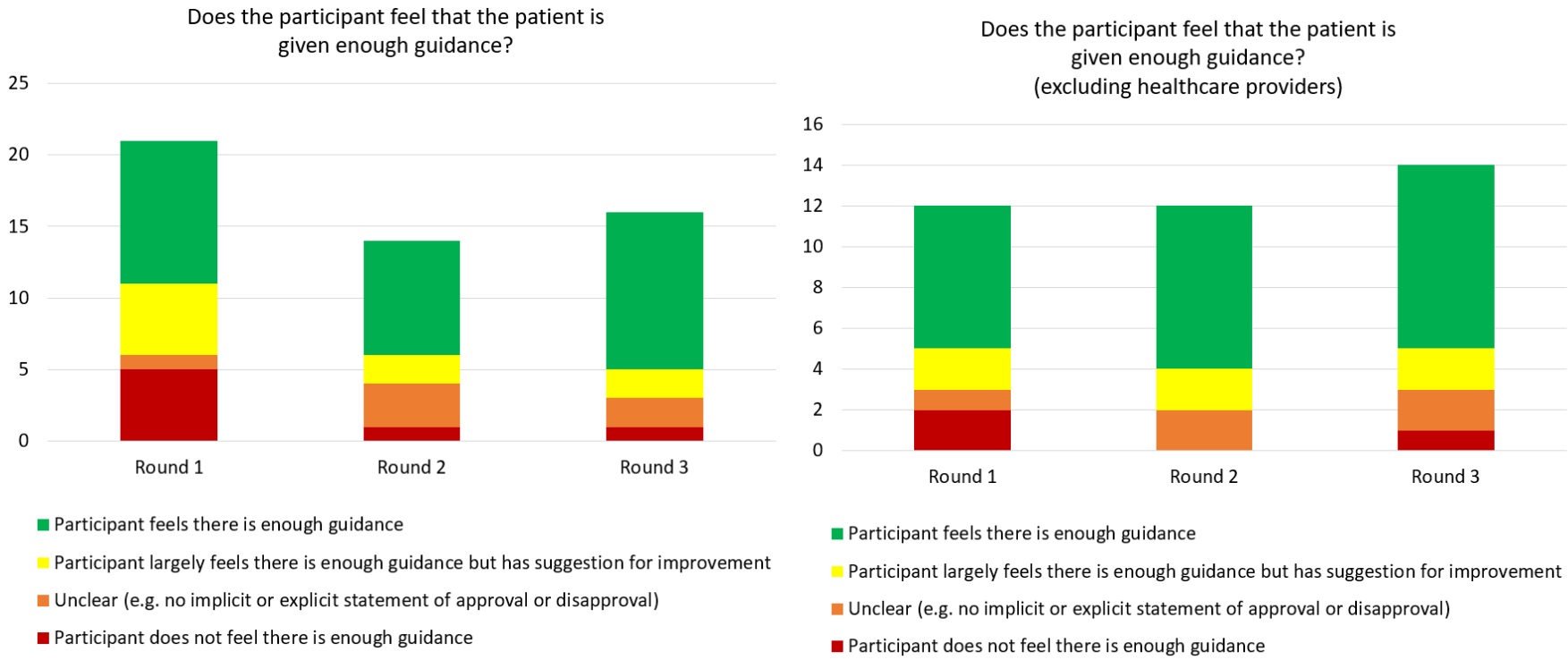

Figure S6

Participant answers to the question “What are your thoughts on the wording of the report and the level of the language used on page 1?” were coded for *participant approval* by 3 independent raters (Fleiss’ kappa 0.7) into the categories indicated in the legend. Visualisation on left panel includes all participants, while right panel excludes healthcare providers.

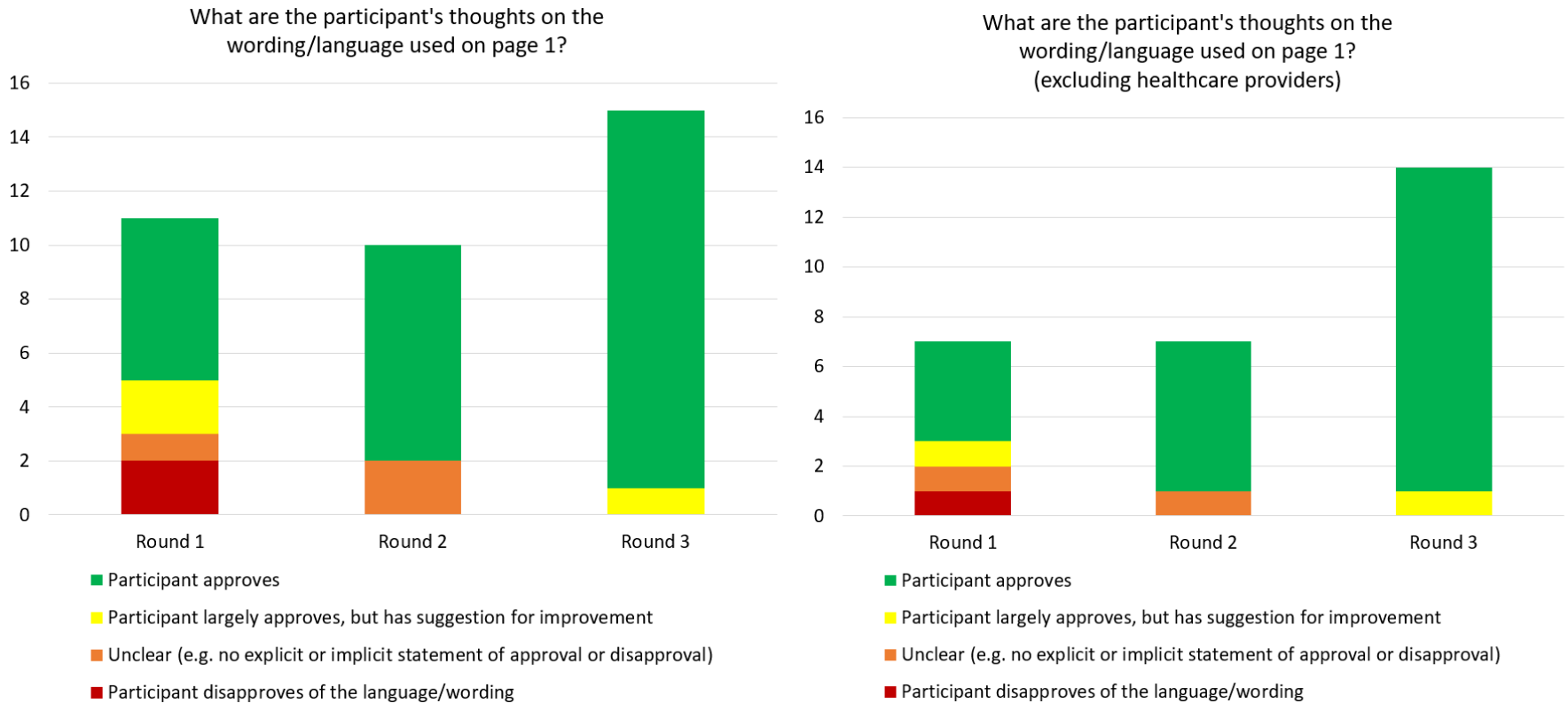

Figure S7

Participant answers to the question “What are your thoughts on the wording of the report and the level of the language used on page 1?” were coded for *confusion* by 3 independent raters (Fleiss’ kappa 0.6) into the categories indicated in the legend. Visualisation on left panel includes all participants, while right panel excludes healthcare providers.

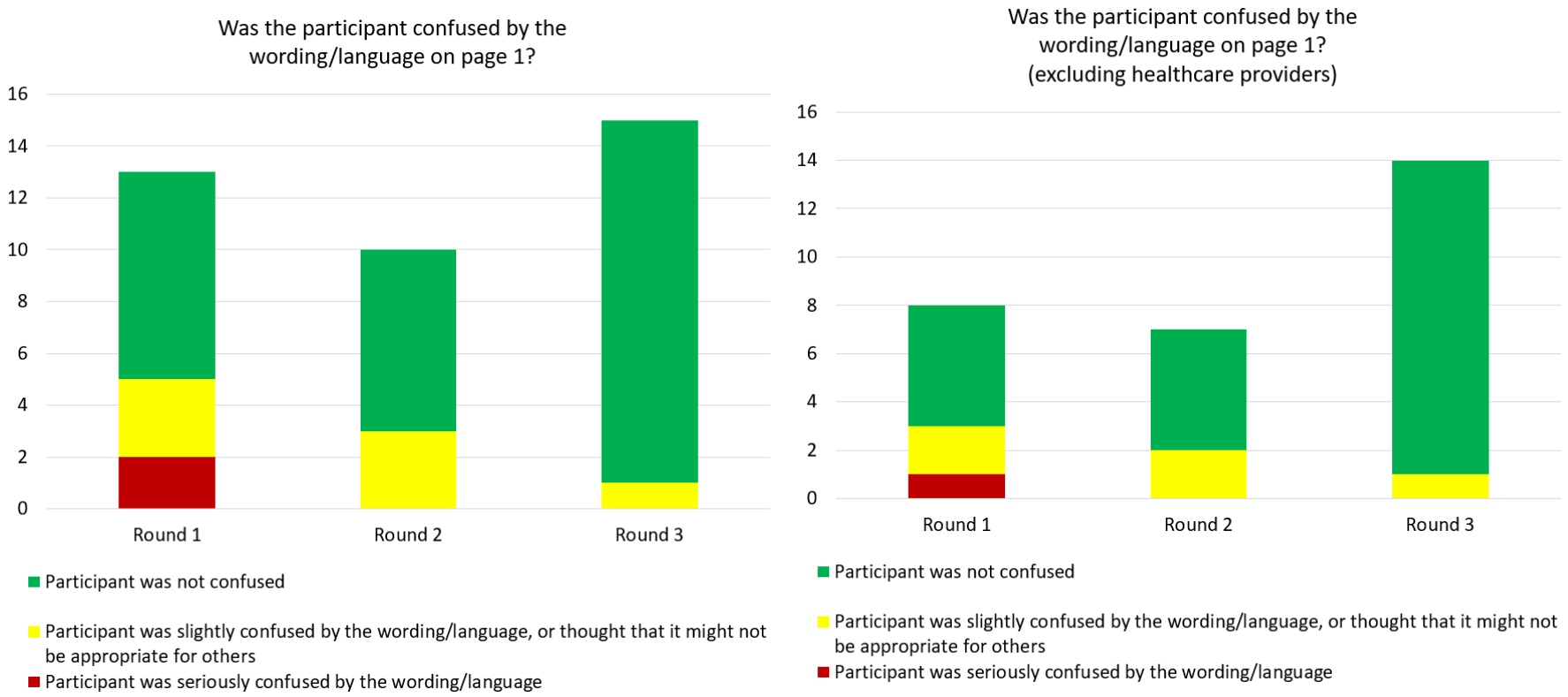

Figure S8

Participant answers to the question “Are there any particular words or phrases that are confusing?” were coded by 3 independent raters (Fleiss’ kappa 0.8) into the categories indicated in the legend. Visualisation on left panel includes all participants, while right panel excludes healthcare providers.

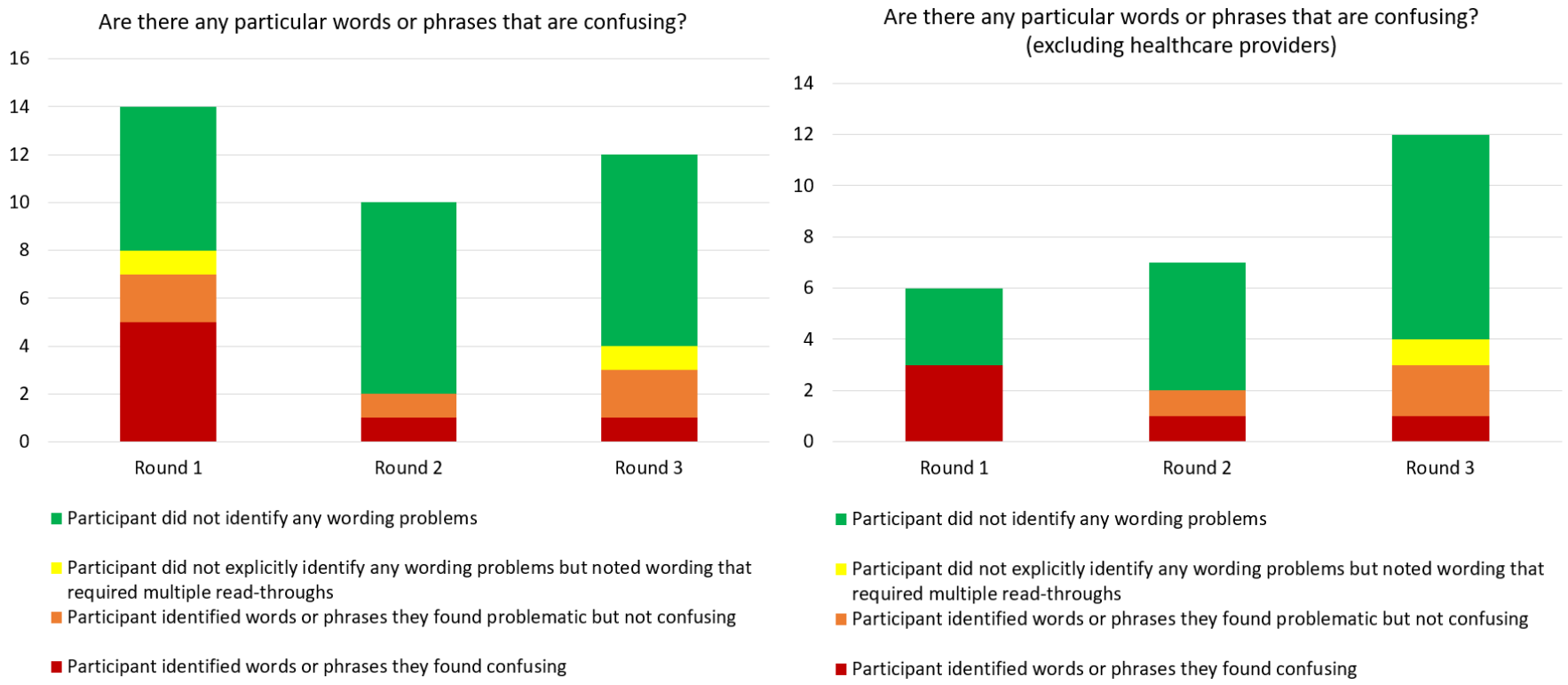

Figure S9

Participant answers to the question “Is there any information that you’d be left wanting to know after reading this report?” were coded by 3 independent raters (Fleiss’ kappa 0.9) into the categories indicated in the legend. Visualisation on left panel includes all participants, while right panel excludes healthcare providers.

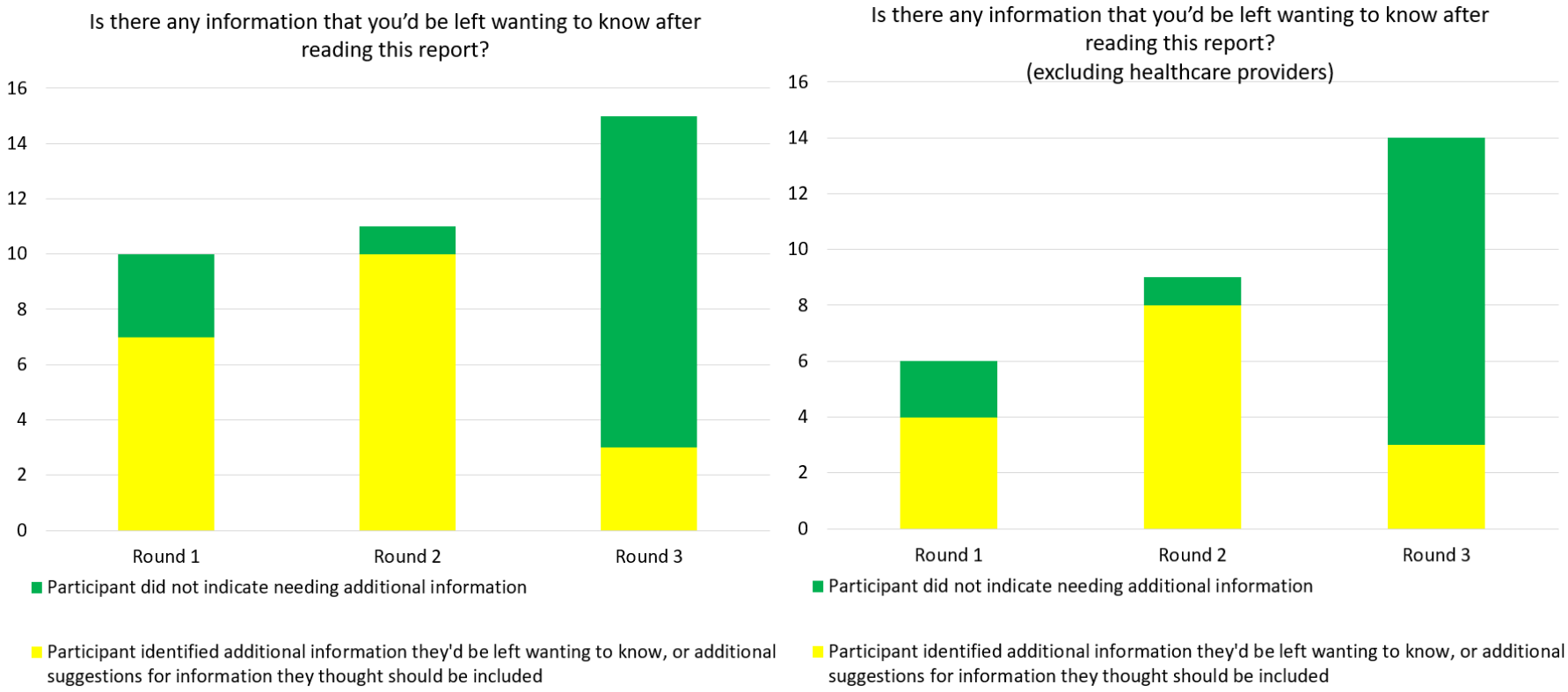

Figure S10

Density plot of communication efficacy.

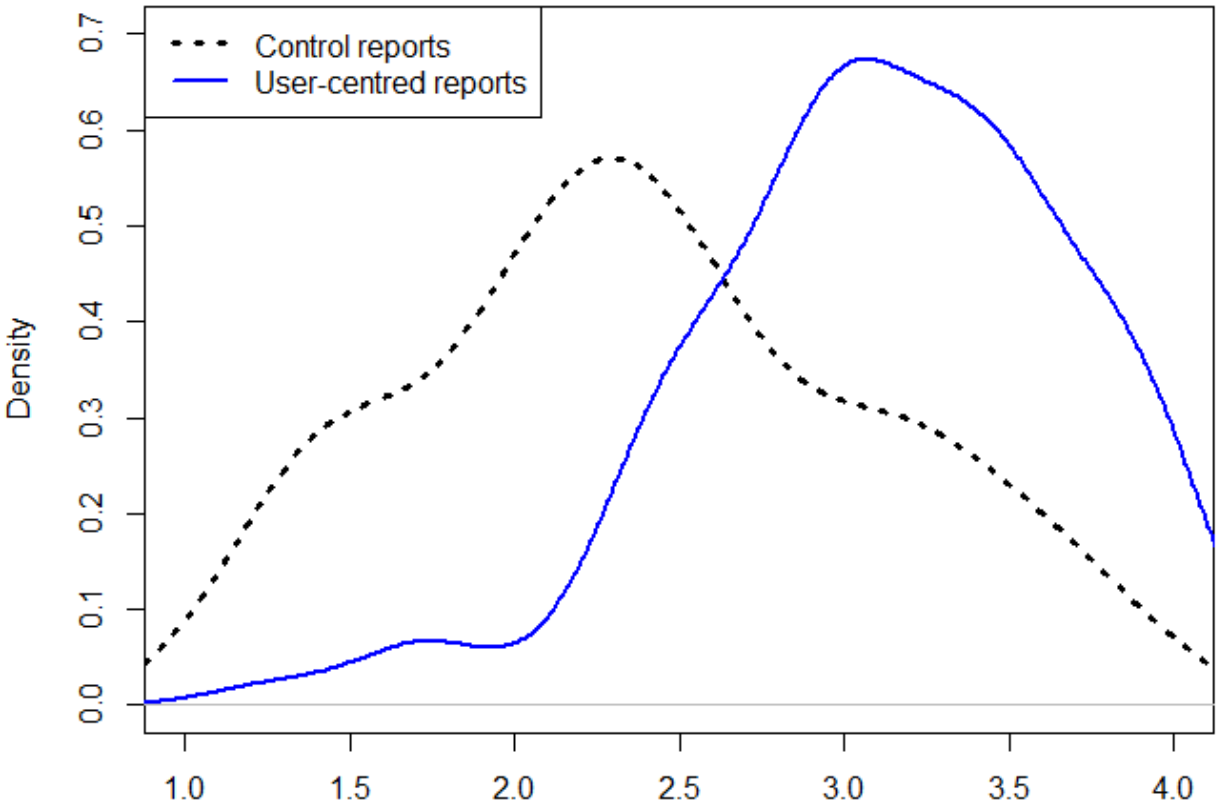

Figure S11

Density plot of subjective comprehension.

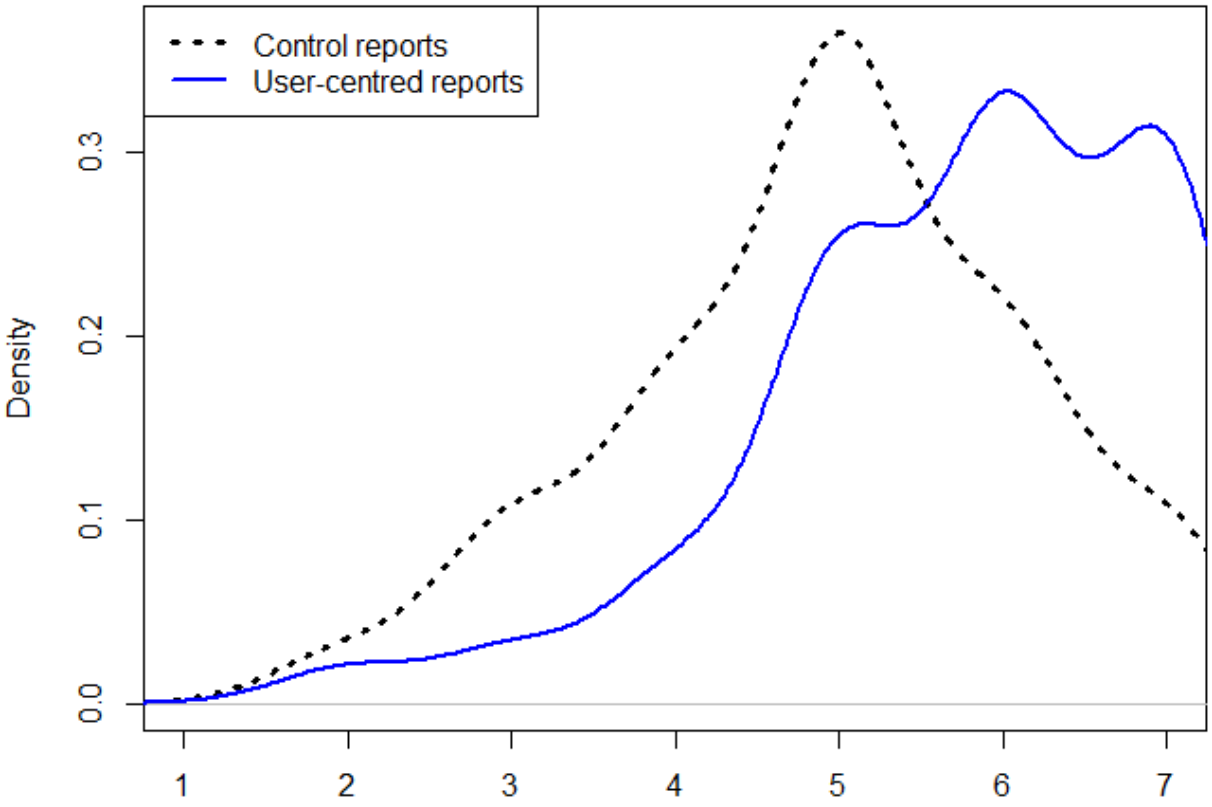

Figure S12

Density plot of objective comprehension.

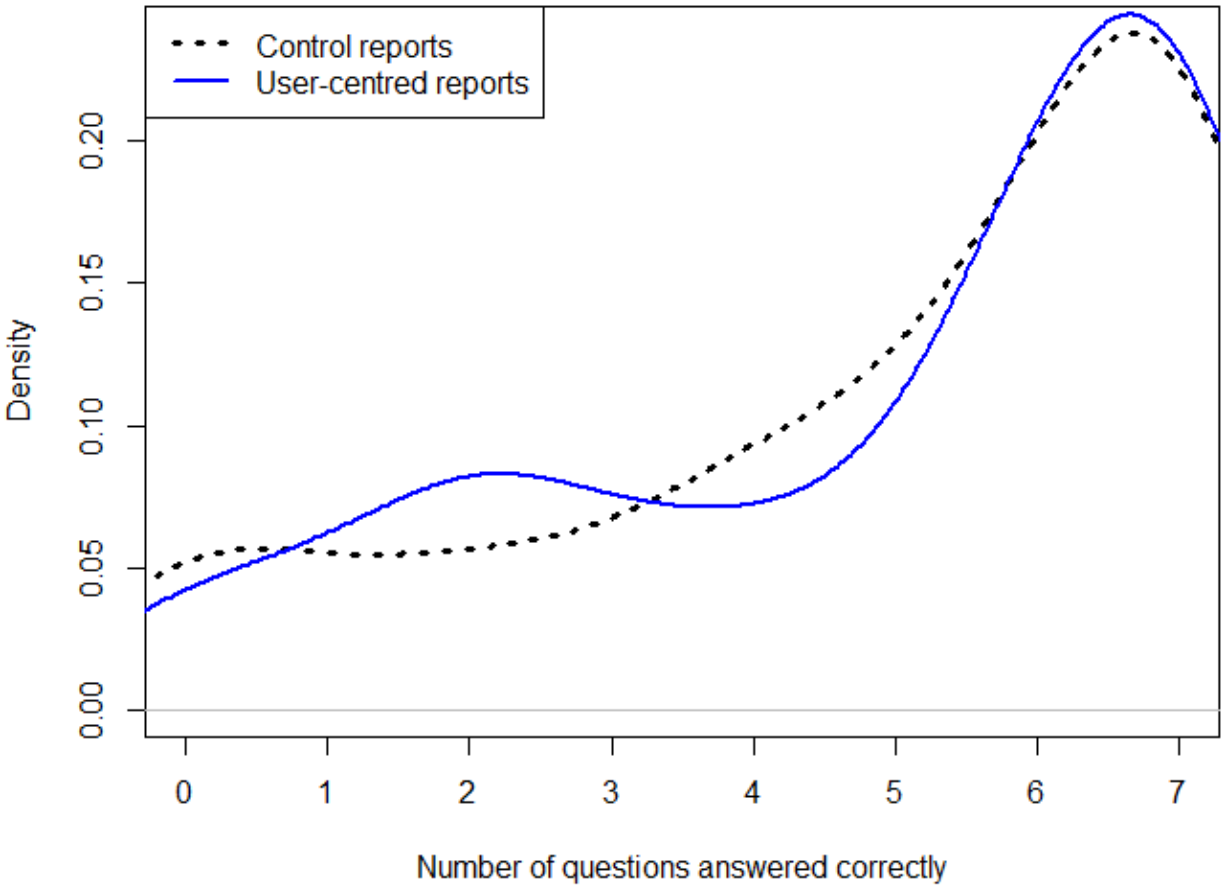

Figure S13

Density plot of subjective clarity.

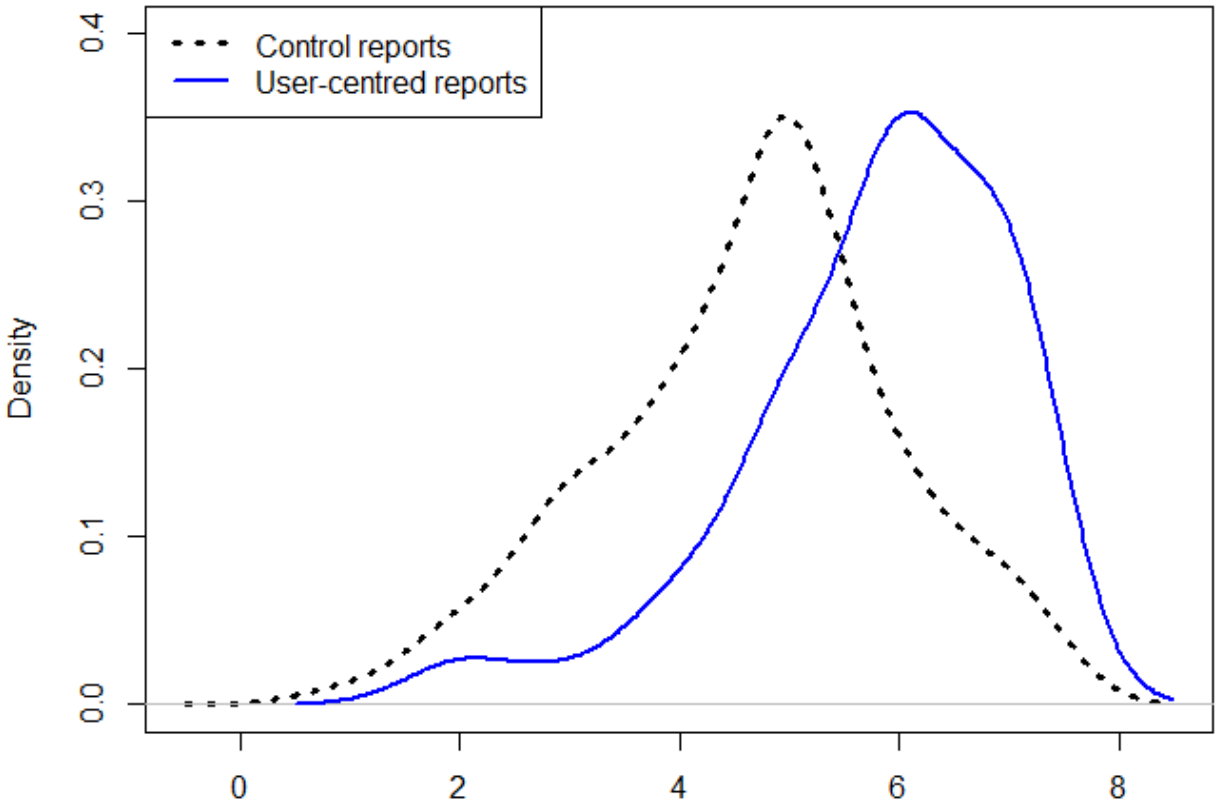

Figure S14

Density plot of subjective trust.

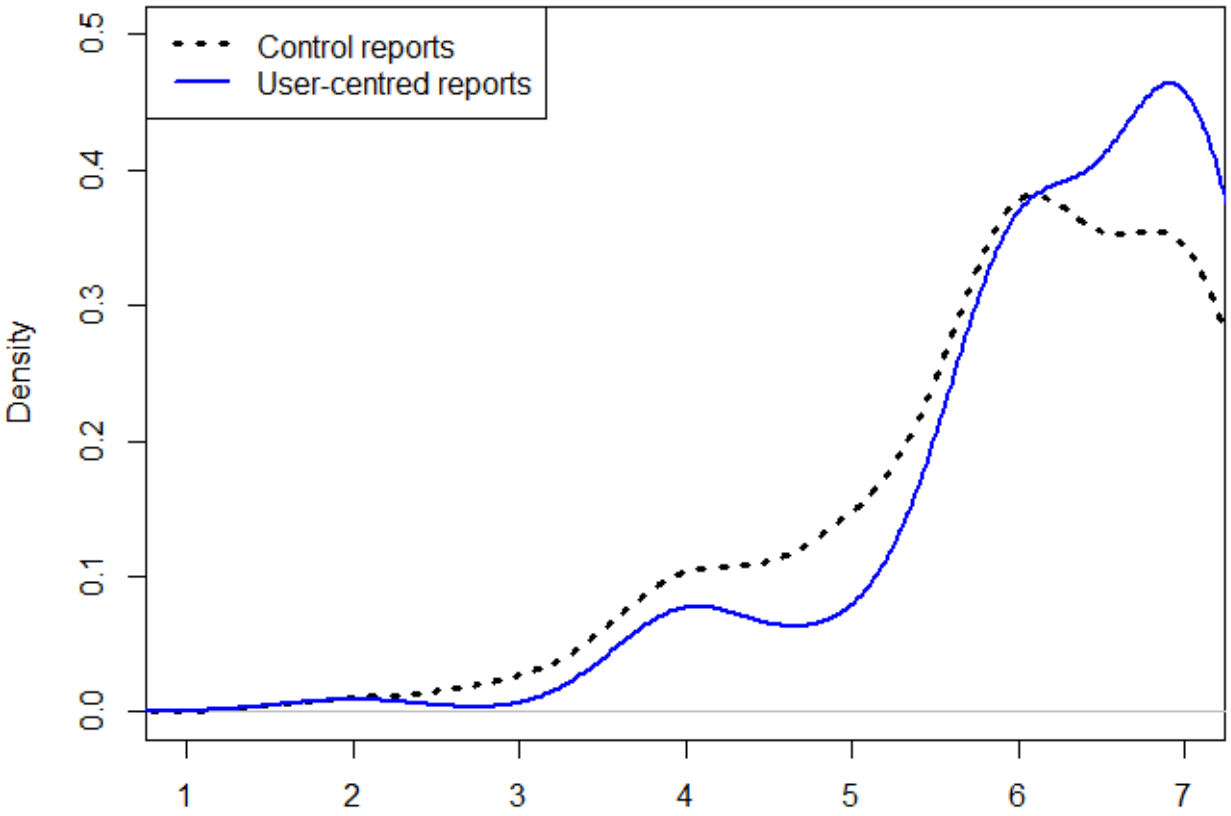

Figure S15

Density plot of actionability.

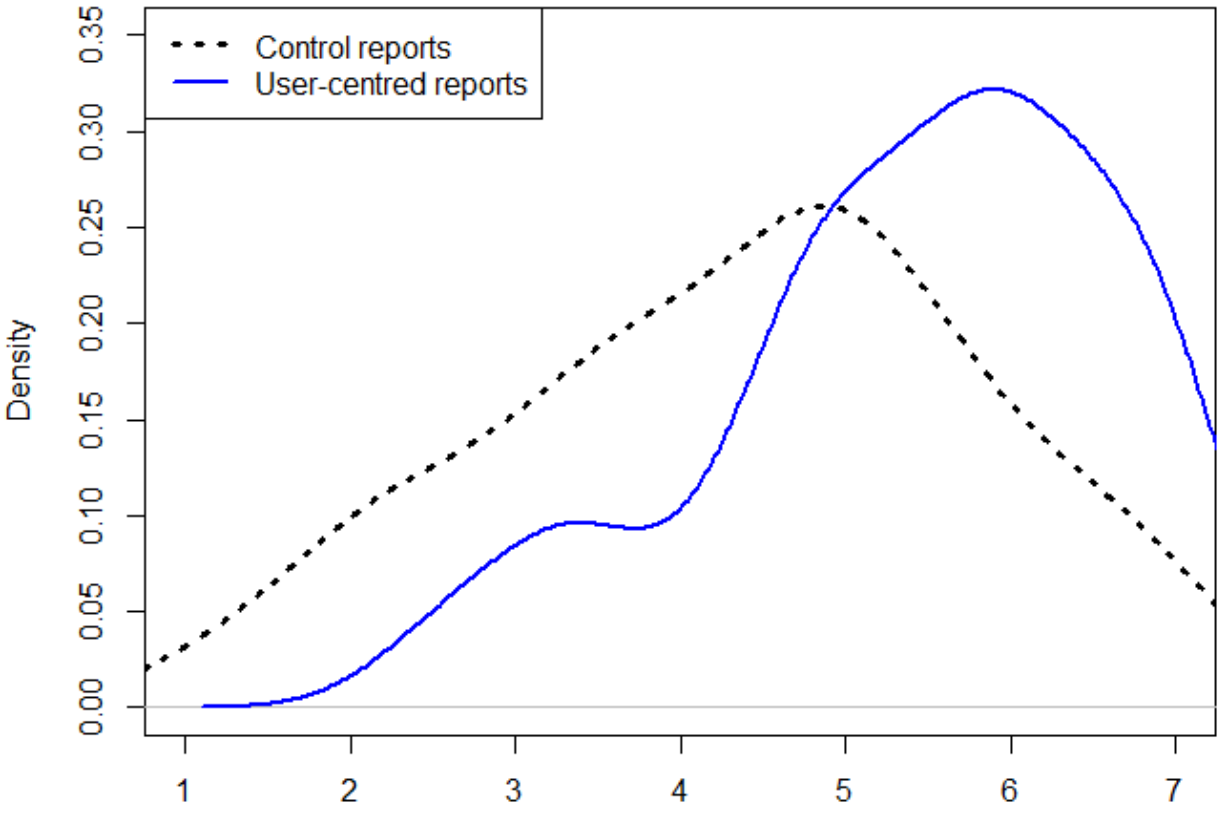

Figure S16

Density plot of ease of understanding of the result summary.

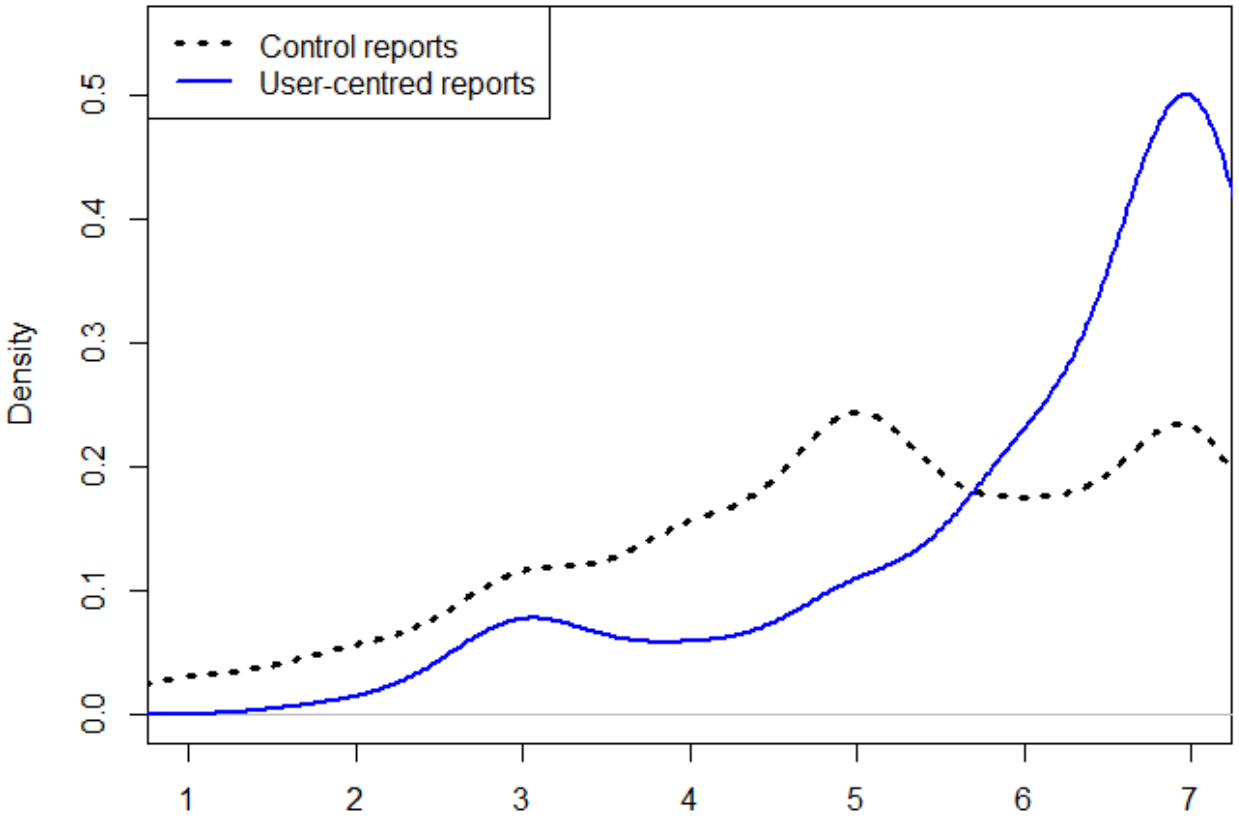

Table S1. Demographics of participants in formative evaluation.

	Round 1		Round 2		Round 3	
Participants	12		8		10	
Age range	22-51		26-46		19-52	
Gender						
Male	4	(33%)	1	(12%)	1	(10%)
Female	8	(67%)	7	(88%)	9	(90%)
Education						
No university	2	(17%)	1	(12%)	3	(30%)
Bachelors	4	(33%)	3	(38%)	6	(50%)
Post-graduate	6	(50%)	4	(50%)	1	(10%)
Health professional?						
Yes	5	(42%)	2	(25%)	1	(10%)
No	7	(58%)	6	(75%)	9	(90%)
Indicated that they themselves had CF or relative with CF? [a]						
No	12	(100%)	8	(100%)	10	(100%)

[a]Participants were not explicitly asked whether they had CF or had a relative with CF, but were asked whether they had experience with cystic fibrosis. 3 participants in Round 1 had cared for patients with CF, 1 indicated having known someone with CF, and 1 mentioned learning about it at school. 1 participant in Round 2 mentioned encountering CF in a clinical science rotation. 1 participant in Round 3 mentioned encountering CF as part of medical studies, and 1 participant mentioned knowing individuals with CF.

Table S2. Demographics of participants in summative evaluation.

	N	%	% in UK population, where known
Gender			
Male	55	(28%)	49% [a]
Female	134	(69%)	51% [a]
Missing	4	(2%)	
Age group			
18-24 years	54	(28%)	31% [b]
25-34 years	62	(32%)	13% [b]
35-44 years	38	(20%)	14% [b]
45-54 years	27	(14%)	14% [b]
55+	8	(4%)	28% [b]
Missing	4	(2%)	
Adults in house			
1	30	(16%)	20% [c]
2	106	(55%)	53% [c]
3	30	(16%)	16% [c]
4+	27	(14%)	11% [c]
Children in house			
0	30	(16%)	As of 2017, 57% of people in UK households lived in households with one or more children [d]
1	106	(55%)	
2	30	(16%)	
3	17	(9%)	
4+	10	(5%)	
Combined income			
Less than £10k	20	(10%)	As of 2017/18 financial year, quintiles of disposable UK household income were £13k, £22k, £29k, £38k, and £69k [e]
£10k to £20k	28	(14%)	
£21k to £30k	35	(18%)	
£31k to £40k	26	(14%)	
£41k to £50k	18	(9%)	
£51k to £60k	18	(9%)	
£61k to £70k	15	(8%)	
£71k to £80k	5	(3%)	
£81k to £90k	7	(4%)	
More than £91k	11	(6%)	
Missing	10	(5%)	
Education			
GCSE or equivalent (e.g., level 2 NVQ)	22	(11%)	Primary/middle school, 19%; GCSE or A-levels, 35%; bachelors and higher, 46% [f]
A-Level or equivalent (e.g., IB or level 3 NVQ)	61	(32%)	
Bachelors (e.g., BA, Bsc)	81	(42%)	
Masters (e.g., MA, MSc)	21	(11%)	
Doctoral (e.g., PhD)	5	(3%)	
Missing	3	(2%)	
Subjective numeracy (1 to 6)			
Less than or equal to 3	21	(11%)	Unknown in UK population. In one large study stratified to mirror the U.S. population, 25th percentile was 3.2, median was 4.2, and 75th percentile was 4.8 [g]
3.01 to 4	52	(27%)	
4.01 to 5	70	(36%)	
5.01 or greater	50	(26%)	
Do you have any personal experience with cystic fibrosis?			
Yes	8	(4%)	
No	185	(96%)	

[a] *Male and female populations: GOV.UK ethnicity facts and figures*, 2018. Available at: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/male-and-female-populations/latest. Accessed June 18, 2019.

[b] Percentages calculated from *Age groups: GOV.UK ethnicity facts and figures*, 2019. https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/age-groups/latest. Accessed June 18, 2019.

[c] Percentage of adults living in *N*-adult households calculated from *CT0774_2011 Census - Age of Household Reference Person (HRP) by number of adults in household - national to local authority leve*l. London: Office for National Statistics, 2018. Calculation excludes the 165 households in England and Wales with 15+ adults (less than .01% of all households). https://www.ons.gov.uk/peoplepopulationandcommunity/housing/adhocs/008208ct07742011censusageofhouseholdreferencepersonhrpbynumberofadultsinhouseholdnationaltolocalauthoritylevel. Accessed June 18, 2019.

[d] Calculated from *Families and households.* London: Office for National Statistics, 2017. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/datasets/familiesandhouseholdsfamiliesandhouseholds. Accessed June 18, 2019.

[e] From Table 2 of *The effects of taxes and benefits on household income, disposable income estimate: 2018.* London: Office for National Statistics, 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/personalandhouseholdfinances/incomeandwealth/bulletins/householddisposableincomeandinequality/yearending2018/relateddata

[f] OECD. Table A1.1 - Educational attainment of 25-64 year-olds (2017): Percentage of adults with a given level of education as the highest level attained", in *The Output of Educational Institutions and the Impact of Learning*, OECD Publishing, Paris, 2018: 54. https://doi.org/10.1787/eag-2018-table14-en. Following up on methodology referenced in table notes, and combining this with UK-specific definitions of ISCED levels (http://gpseducation.oecd.org/Content/MapOfEducationSystem/GBR/GBR_2011_EN.pdf) reveals that attainment of GCSE or A-levels corresponds to columns 5 and 6.

[g] Zikmund-Fisher BJ, Smith DM, Ubel PA, Fagerlin A. Validation of the subjective numeracy scale: Effects of low numeracy on comprehension of risk communications and utility elicitations. *Medical Decision Making* 2007 Sep; 27(5):663-71.

Table S3. Risk comprehension questions presented in rounds 2 and 3 of interviews.

Question	Correct answer	Number answering correctly, round 2	Number answering correctly, round 3
For a random person in the UK who has never been tested for CF, what are their chances of being a carrier?	1 in 25 (4%)	7 of 8 (first answer given) 8 of 8 (after self-correction)	10 of 10 (first answer given) 10 of 10 (after self-correction)
And what are their chances of not being a carrier?	24 in 25 (96%)	7 of 8 (first answer given) 8 of 8 (after self-correction)	9 of 10 (first answer given) 10 of 10 (after self-correction)
If both you and your partner are carriers, what is the chance in each pregnancy of having a child that has CF?	1 in 4 (25%)	8 of 8 (first answer given) 8 of 8 (after self-correction)	9 of 10 (first answer given) 10 of 10 (after self-correction)
If you are a carrier and you have a child with someone who has never been tested, what are the chances then that the child will have CF?	less than 1 in 100 (less than 1%)	5 of 8 (first answer given) 5 of 8 (after self-correction)	8 of 10 (first answer given) 10 of 10 (after self-correction)
If both you and your partner are carriers, what is the chance in each pregnancy of having a healthy child?	3 in 4 (75%)	8 of 8 (first answer given) 8 of 8 (after self-correction)	7 of 10 (first answer given) 9 of 10 (after self-correction)

Table S4. Summary of main changes to reports made from version 1 to version 2.

Section	Changes
Reason for Test	• Black to blue • Bold • Acronym "CF" used
About The Test	• Section added to explain inheritance and meaning of "carrier" • Acronym "CF" introduced
Results Box	• "Result" to "Your Result" – bold • "gene changes" to "gene alterations"
What This Result Means	• "What This Result Means" to "What This Result Means for You" • Explanation of "carrier" removed as covered in About The Test • "single altered Cystic Fibrosis gene" to "one copy of your CFTR genes" [positive reports] • "not a carrier of CF" to "not a known carrier of CF" [positive reports] • "gene changes" to "gene alterations" • "assuming that you are of Northern European origin and that the family relationships stated in the referral are correct" removed [negative reports] • General wording and sentence structure changed to improve explanations, grammar and flow; key risk figures represented with both "X in Y" and as a percentage • Sentence order rearranged to improve comprehension of risk, with some figures removed all together and some risk formats altered
Next Steps	• Text bold and presented as bullet points (using dashes) • "…but if you have questions about it, talk to your doctor" added after "You do not need to do anything as a result of this test" • "Take this report with you to any appointments" added [Positive / Partner p.Phe508del]
More Information and Support	• "If you don't have access to the internet, contact the doctor who ordered your test" removed • Phone number for Cystic Fibrosis Trust helpline added
Layout / Formatting	• Section headings bold • Separate line for each point • More Information and Support section moved under, rather than adjacent to, Next Steps.
For Your Records	• "For Your Records" bold • "If there is anything you do not understand, your doctor will help you to interpret this information" to "The information on this page is for health professionals. It is not essential that patients read this section."
Test Methodology	• Risk of a false positive/negative added • Each reference listed on a new line
Full Interpretation	• "gene change" to "gene variant" • "assuming that the family relationships are as stated" removed [negative reports]
Layout / Formatting	• Full Interpretation section moved above Test Methodology

Table S5. Summary of main changes to reports made from version 2 to version 3.

Section	Changes
Top Section	• Order of patient details changed to reflect usual laboratory use of information i.e. name followed by date of birth. (also on p.2) • "Copies to" added • Details in "Test carried out by" altered to reflect usual laboratory use of information: • "Name" removed • "Date of Test" replaced with "Date received" and "Date Reported" • "Signature" replaced with "Authorised by"
About The Test	• Heading bold
Results Box	• "No Cystic Fibrosis gene alterations detected" to "No common cystic fibrosis gene alterations detected" [Negative / Partner p.Phe508del]
What This Result Means for You	• "each pregnancy" made bold [positive reports & Negative / Partner p.Phe508del] • "affected with CF" to "have CF" [positive reports & Negative / Partner p.Phe508del] • "someone who is not a known carrier of CF" to "someone who has not been tested for CF" [positive reports] • "(some risk remains as your partner may be a carrier but not know)" added [positive reports] • "No alterations were detected" to "No alterations were detected, so you are not a carrier of any of the alterations we tested for" [negative reports] • "This may require an additional test" added [Negative / Family history] • "This is low, so prenatal testing is not offered" removed [Negative / Partner p.Phe508del] • Some wording changed to improve explanations, grammar and flow. • Some risk figures removed
Next Steps	• All text bold • Dashes replaced with bullet points • "we could do a more accurate test" to "we could investigate further" [Negative / Family history] • Alternative options for relatives living in/outside of East Anglia moved to page 2 and replaced with "If your relatives would like to be tested, they should ask their GP about CF carrier testing"
More Information and Support	• Phone number for the Regional Genetics Service added • "call" to "phone" • "http://" removed from web addresses • *Note.* By request of the Cystic Fibrosis Trust, the website but not the helpline number will appear in the final version of the reports.
Layout / Formatting	• About The Test section moved under, rather than above, Your Result box • Dashed lines between sections removed • Pattern of pale blue shading altered to aid visual separation of sections (Design 2) • Incorrect use of capital letters for "cystic fibrosis" amended throughout

For Your Records	• All text in box made bold
Full Interpretation	• "i" in "interpretation" capitalised in heading • "assuming that he is of Northern European origin" removed • "John Doe's CF carrier risk could be determined significantly more accurately if details of the familial CFTR gene variants were known" to "If the specific familial CFTR gene variant were known, we could assess John Doe's CF carrier risk directly with a targeted test" [Negative / Family history] • Paragraph added about carrier testing and where to send samples
Layout / Formatting	• Technical results put in a box

Table S6. Usability problems uncovered through user testing.

Round	Severity[a]	Issue
1	4	Population risk presented in a confusing, arguably misleading way which implied to some participants that the recipient's carrier risk had been "reduced" from 1 in 25 to 1 in 18 (which was not the case and is not a reduction)
	3	Ethnicity/family relationships disclaimer on p. 1 caused consternation
	3	Basic result (carrier vs. likely noncarrier status) not always understood
	3	Percentage of CFTR gene variants not covered by the test (15%) confused with percentage chance of not being a carrier
	3	Reference to "gene changes" misinterpreted ("Can genes change throughout the lifecourse or something? I thought you're kind of born with it or you're not")
	2	Concern about *why* there was residual risk of being a carrier on negative reports
	2	No phone numbers provided in "More Information and Support" for individuals without internet access
	2	Annoyance at imprecision of the "low" risk of being a carrier on negative reports
	2	Several participants felt that "You do not need to do anything as a result of this test" alone left them hanging, requested more information about who to contact with questions
	1	'Next Steps' section did not remind recipient to take this report to future appointments with the Clinical Genetics Service
	1	Various cosmetic features made it unnecessarily difficult to visually distinguish between different sections and between recommended "next steps"
2	3	Ethnicity disclaimer on p. 2 caused consternation
	3	For negative reports, concern about the 15% of UK CFTR gene variants not covered by the test that seemed highly disproportionate to risk of being a carrier (less than 0.2%); 15% of CFTR gene variants not covered by the test potentially still being confused with the risk of carrying a pathogenic variant
	2	Some confusion from unfortunate coincidence of "1 in 25 (4%)" followed by "1 in 4 (25%)" in immediately following sentence

	2	Concern that recipients would want a better explanation of exactly why there is a 1 in 4 chance that any given child of two carriers will have cystic fibrosis
	2	Participants did not notice heading indicating that page 2 was primarily for their clinician and did not need to be read and understood by patients
	2	More clarity requested on why the report cannot be more definitive
	2	Phone number of Regional Genetics Service not provided
	2	Confusion about how to interpret "affected with CF" in context of interviewer questions; possibility of confusion since this phrase is used on reports as well
	1	Differentiating people living inside vs. outside East Anglia is confusing, as next step for people whose relatives would like to be tested is to discuss with GP in either case
	1	Easy to skip over "About the Test" section, as eye is drawn to the result first
	1	Table on p. 2 hard to read without borders
	1	Various requests related to increasing visual clarity (too busy, too many fonts, dashed lines not necessary, needs more white space, etc.)
3	2	Mentioning that results "can be upsetting and difficult to take in" on negative reports confusing
	2	Participants did not notice heading indicating that page 2 was primarily for their clinician and did not need to be read and understood by patients
	2	More clarity requested on why the report cannot be more definitive
	2	Confusion about which 'doctor' to return to with questions
	2	Some confusion about what CFTR means (though no confusion about the fact that it referred to a gene)
	1	Could be made clearer which page is the front
	1	"If you plan to have children, CF carrier testing can be offered to your partner before any pregnancy" may be more visible if placed in "Next Steps" section, arguably a more appropriate place for it, rather than current location
	1	Requests to further increase separation between different sections

[a]We used a severity rating scale borrowed from Rubin (1994)[b], which we adapted to our specific case to make issues easier to classify:

1: "The problem occurs rarely, can be circumvented easily, or is dependent on a standard that is outside the product's boundaries. Could also be a cosmetic problem."

2: “The user will be able to use the product, but may have to undertake some moderate effort to get around the problem.” We considered this to include wishes for additional information or clarity that could be satisfied by asking one’s GP.

3: “The user will probably use or attempt to use the product, but will be severely limited in his or her ability to do so.” We considered this to include issues that could leave recipients with a serious misconception.

4: “The user is not able to or will not want to use a particular part of the product because of the way that the product has been designed and implemented.” We had one case of this in Round 1, resulting from an issue that would have been a (3) if not for one user’s strong negative emotional reaction.

[b]Rubin J. Handbook of usability testing: how to plan, design and conduct effective tests. New York, NY: John Wiley & Sons, 1994.

Table S7. Examples of how specific usability problems were addressed.

Issue	Response
Confusion over whether CF "gene changes" – a phrase introduced as a plain-English alternative to "pathogenic variants" – could occur in the future ("What does it mean by no cystic fibrosis gene changes detected? Can genes change throughout the life course or something? I thought you're kind of born with it or you're not.")	"Alterations" employed as plain-English alternative to "changes" or "variants"
Information about the 85% of pathogenic variants covered by the panel was confused with the risk of being a carrier (e.g. "There's a 15% chance that you're still a carrier… I could be in that 15%.")	Restated for clarification; ultimately removed 85% statistic from patient-facing page altogether as the restatement did not solve the issue
Confusion around the juxtaposition of a sentence stating that the risk is now known to be lower than their *a priori* risk ("The fact that we did not detect any changes reduces the chance that you carry a CF gene change slightly, to 1 in 18") and an unrelated sentence earlier in the report stating the population risk ("In the UK population, around 1 in 25 people are carriers of CF"); this was interpreted as a risk of 1 in 25 that had been "reduced" to a (greater) risk of 1 in 18.	Sentences rephrased for clarity. The further confusion caused by comparing two risks of differing denominators (given that the risk with the larger denominator was misinterpreted as the higher risk in at least one case) was addressed by expressing carrier risk as a percentage and as "1 in 18," and the *a priori* risk as a percentage only
Confusion from unfortunate coincidence of "1 in 25 (4%)" followed by "1 in 4 (25%)" in immediately following sentence	Moved the statement about the 4% of individuals who are carriers of CF in the UK population to a more contextually appropriate place later in the report

Table S8. Performance of user-centered reports vs. standard reports, summarized. The user-centered report is deemed "better" or "worse" when differences are statistically significant (adjusted $\alpha = .01$). All values other than percentages are means.

	Performance of user-centered report (user-centered report vs. standard report)
Key objectives	
Risk probability comprehension scores	**Equivalent** (4.95 vs. 4.94)
Subjective comprehension scores	
Subjective understanding	**Better** (5.74 vs. 4.94)
Subjective clarity	**Better** (5.78 vs. 4.65)
Communication efficacy scores	**Better** (3.11 vs. 2.41)
Exploratory objectives	
Trust scores	**Equivalent** (6.23 vs. 5.92)
Actionability scores	**Better** (5.41 vs. 4.37)
Risk probability interpretation (What % of interpretations were clearly wrong[a]?)	**Equivalent** (5% vs. 7% wrong)
Visibility of result summary (What % of the time was result summary noticed?)	**Worse** (73% vs. 92%)
Ease of understanding result summary scores	**Better** (6.05 vs. 5.00)
Primary goal: Key objectives	
Better performance on at least one; worse performance on none	**Met**
Secondary goal: All objectives	
Better performance on at least one; worse performance on none	**Not met**

[a] "Clearly wrong" interpretations were beliefs that the first child of a couple receiving a positive report would "definitely" or "definitely not" have CF, and beliefs that the first child of a couple receiving a negative report would "definitely" or "likely" have CF.

Table S9. Subgroup analyses (Mann-Whitney U-tests).

	Standard report		User-centered report				
	Mean	SD	Mean	SD	U	Cohen's d	p-value
Participants who did not attend university (n = 83)							
Risk probability comprehension	4.61	2.43	4.29	2.53	872	-.13	.72
Subjective understanding	4.78	1.26	5.50	1.26	563	.57	.01
Subjective clarity	4.61	1.32	5.91	1.26	382	1.0	<.001
Communication efficacy	2.43	0.65	3.10	0.57	354	1.1	<.001
Actionability	4.41	1.33	5.23	1.29	554	.62	.01
Ease of understanding result summary	4.92	1.63	5.97	1.34	514	.69	.002
Participants with low subjective numeracy[a] (n = 80)							
Risk probability comprehension	3.90	2.36	3.62	2.46	853	-.12	.60
Subjective comprehension	4.63	1.16	5.28	1.36	538	.52	.01
Subjective clarity	4.46	1.14	5.49	1.41	411	.80	<.001
Communication efficacy	2.29	0.69	2.99	0.69	368	1.0	<.001
Actionability	3.97	1.35	5.17	1.25	420	.93	<.001
Ease of understanding result summary	4.68	1.57	5.79	1.47	470	.73	<.001
Men (n = 55)							
Risk probability comprehension	4.63	2.40	5.29	2.23	304	.28	.20
Subjective comprehension	4.48	1.34	5.96	1.04	141	1.2	<.001
Subjective clarity	4.26	1.40	5.96	1.04	122	1.4	<.001
Communication efficacy	2.38	0.64	3.14	0.51	132	1.3	<.001
Actionability	4.28	1.40	5.56	1.18	184	.99	.001
Ease of understanding result summary	4.81	1.84	6.43	1.03	184	1.1	<.001
Women (n = 134)							
Risk probability comprehension	5.00	2.28	4.87	2.34	2316	-.06	.75
Subjective comprehension	5.15	1.13	5.66	1.23	1645	.43	.006
Subjective clarity	4.81	1.27	5.72	1.25	1282	.72	<.001
Communication efficacy	2.43	0.73	3.13	0.56	1010	1.08	<.001
Actionability	4.42	1.51	5.35	1.23	1412	.67	<.001
Ease of understanding result summary	5.01	1.58	5.96	1.39	1420	.63	<.001

[a] Defined as falling below the 50th percentile of Zikmund-Fisher et al.'s nationally representative sample of U.S. participants. Zikmund-Fisher BJ, Smith DM, Ubel PA, Fagerlin A. Validation of the subjective numeracy scale: Effects of low numeracy on comprehension of risk communications and utility elicitations. *Medical Decision Making* 2007 Sep; 27(5):663-71. In our data, subjective numeracy was only mildly correlated with risk probability comprehension (r = .4) and had significant but even weaker correlations with other variables.